ACRYSOF® IQ ReSTOR® TORIC MULTIFOCAL INTRAOCULAR LENS

FOR

PRIMARY IMPLANTATION FOR VISUAL CORRECTION OF APHAKIA SECONDARY TO REMOVAL OF A CATARACTOUS LENS

EXECUTIVE SUMMARY FOR NOVEMBER 14, 2014 MEETING OF OPHTHALMIC DEVICES PANEL OF MEDICAL DEVICES ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
APPLES	*Assessment of Photic Phenomena and Lens EffectS*
BCDVA	Best corrected distance visual acuity
BCNVA	Best corrected near visual acuity
cm	Centimeters
CD/M^2 cd/m^2	Candela per meter squared
CI	Confidence interval
CPD, cpd	Cycles per degree
D	Diopter
DCNVA	Distance corrected near visual acuity
EFA	Exploratory Factor Analysis
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
FE	Fundus examination
IDE	Investigational Device Exemption
IOL	Intraocular lens
IOP	Intraocular pressure
logMAR	Logarithm of the minimum angle of resolution
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mm	Millimeter
N, n	Number
OD	Right eye
Op	Operative
OS	Left eye
OU	Both eyes
OUS	Outside of the United States
OVD	Ophthalmic Viscosurgical Device
PALO	Photographic Assessment of Lens Orientation
PCO	Posterior capsular opacification
PMA	Premarket Approval
PRO	Patient reported outcome
PT	Preferred Term
PXF	Pseudoexfoliation
RPE	Retinal pigment epithelium
RSVP	Refractive Status and Vision Profile Instrument
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

Abbreviation	Definition
SD	Standard deviation
SE	Standard error
SILVER	*Spectacle Independence Lens Vision Evaluation and Repurchase*
SLE	Slit lamp examination
SPE	Safety and performance endpoints
SSI	Secondary surgical intervention
UADE	Unanticipated Adverse Device Effect
UCDVA	Uncorrected distance visual acuity
UCI	Upper confidence interval
UCIVA	Uncorrected intermediate visual acuity
UCL	Upper confidence limit
UCNVA	Uncorrected near visual acuity
US	United States
UV	Ultraviolet
VA	Visual acuity
YAG	Yttrium aluminum garnet laser

1 EXECUTIVE SUMMARY

In the US, more than 3 million cataract surgeries are performed each year. For patients undergoing cataract surgery with preexisting corneal astigmatism of 0.75 D or greater, a multifocal IOL is needed that corrects aphakia, reduces astigmatism, and increases the rate of spectacle independence by providing functional uncorrected near, intermediate and distance vision. The AcrySof® IQ ReSTOR® Toric Multifocal Intraocular Lens (hereafter referred to as the ReSTOR Toric IOL) provides patients such an IOL.

As illustrated in Figure 1, the ReSTOR Toric IOL combines in a single lens two clinically studied, FDA approved and globally marketed IOL technologies, the AcrySof ReSTOR Multifocal IOL and the AcrySof Toric IOL, for which the safety and effectiveness profiles are well established. The multifocal feature of the ReSTOR Toric IOL provides correction of presbyopia (i.e., by providing near and intermediate, as well as distance vision), while the toric feature of the IOL provides correction of astigmatism. The ReSTOR Toric IOL was developed using the same lens platform as the approved IOLs and the same AcrySof material that has been used in over 75 million patients since its introduction to the market in 1994. The indications for use of the ReSTOR Toric IOL is a combination of the approved indications of the two technologies.

Figure 1. ReSTOR + Toric = ReSTOR Toric

ReSTOR Multifocal IOL	Monofocal Toric IOL	ReSTOR Toric IOL
Indications for Use: The AcrySof® ReSTOR® Apodized Diffractive Posterior Chamber Intraocular Lens (IOL) is intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. The lens is intended to be placed in the capsular bag.	Indications for Use: The AcrySof® IQ Toric posterior chamber intraocular lenses are intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and pre-existing corneal astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia, who desire improved uncorrected distance vision, reduction of residual refractive cylinder and increased spectacle independence for distance vision.	Indications for Use: The AcrySof® IQ ReSTOR® Multifocal Toric Posterior Chamber Intraocular Lens (IOL) are intended for primary implantation for the visual correction of aphakia **and pre-existing astigmatism** secondary to removal of a cataractous lens in adult patients **with and without presbyopia, who desire near, intermediate and distance vision**, **reduction of residual refractive cylinder** and **increased spectacle independence**. The lens is intended to be placed in the capsular bag.

The ReSTOR Toric IOL is commercially available in the European Union, Australia, Canada, Japan, and many other countries within Central and South America, the Middle East, and the Far East. More than 93,000 units of the ReSTOR Toric IOL have been distributed in countries outside of the United States since June 2010.

Alcon submitted the findings from the development program, including data from the confirmatory clinical study, Clinical Study C-09-036, to the FDA in an application supporting approval of the ReSTOR Toric IOL in the US. Clinical Study C-09-036 was a non-randomized, parallel-group, prospective trial that was intended to show that the addition of the toric surface to the ReSTOR Multifocal IOL would offer patients with ≥ 0.75 D of astigmatism similar efficacy and safety outcomes as those expected with a control multifocal lens in patients with < 0.75 D of astigmatism. Clinical Study C-09-036 demonstrated that the ReSTOR Toric IOL:

- provides patients with near, intermediate and distance vision,
- corrects astigmatism, and
- provides patients with increased spectacle independence.

No additional risks were identified following the implantation of the ReSTOR Toric IOL relative to the risks associated with the implantation of the Control IOL (ReSTOR Multifocal IOL with a +4.0 D add power).

In commercial use outside of the United States, there have been no significant changes to product labeling or product use in any country, and there have been no unanticipated adverse device effects (UADEs) reported. Adverse events reported during commercial distribution are consistent with those seen in Clinical Study C-09-036. In addition, no change to the benefit to risk profile has resulted from the commercial experience.

This briefing document reviews the findings from the device development program and presents the effectiveness and safety experience observed in Clinical Study C-09-036.

1.1 TREATMENT OF APHAKIA AND ASTIGMATISM

When treating cataract patients, an ophthalmologist must correct surgical aphakia (the lack of the natural lens of the eye after cataract removal), spherical power errors (myopia or hyperopia), cylindrical power errors (astigmatism), and presbyopia as applicable. This is necessary to provide near, intermediate, and distance vision for patients with less dependence on spectacles after cataract surgery.

Astigmatism is a variation in the shape or curvature of the cornea and, if left untreated, astigmatism can cause blurred vision at all distances. More than 50% of the patients who undergo cataract surgery have corneal astigmatism ≥ 0.75 D, which may significantly limit an optimal visual outcome if left uncorrected (Riley 2001, Ferrer-Blasco 2009).

Currently, after cataract surgery, astigmatic patients typically receive a monofocal or monofocal toric IOL and then rely on other corrective aids such as glasses to provide near vision. If a monofocal (non-toric) IOL is used, glasses are needed to correct the residual astigmatism in addition to providing near vision. Alternatively, the patient might undergo a secondary surgical procedure to be less dependent on their glasses after their cataract surgery. Multifocal IOLs are not indicated for patients having greater than 1.0 D of astigmatism, and, therefore, are usually not an option for astigmatic patients.

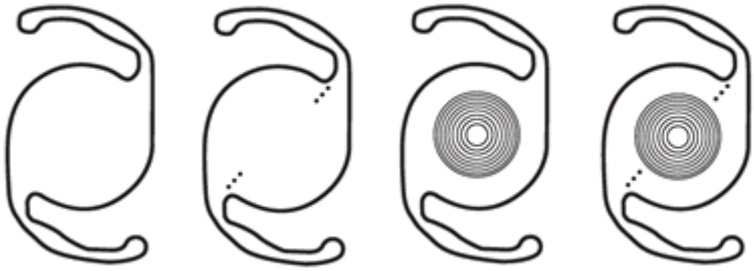
Patients who are seeking to be less dependent on their glasses after cataract surgery desire a single multifocal intraocular lens that can correct for spherical error, astigmatism, and near vision (i.e. presbyopia), and reduce or eliminate the need for secondary procedures. A multifocal toric IOL such as the ReSTOR Toric IOL would provide patients in the US an option to correct presbyopia and astigmatism with one multifocal IOL without requiring additional surgical procedures.

1.2 OVERVIEW OF RESTOR TORIC IOL

The ReSTOR Toric IOL was developed using the same AcrySof single-piece platform design as the AcrySof ReSTOR Multifocal IOL (PMA P040020; hereafter referred to as the Control IOL) and the AcrySof Monofocal Toric IOL (P930014/S015, S016, and S045). Both IOLs are made using the AcrySof material which has a long history of safety and effectiveness. Over 75 million lenses have been sold using the AcrySof technology worldwide. Clinical studies affirmed the safety and effectiveness of both IOL types in order to support approval and marketing in the US, Europe, Japan, and other countries. Both the Control IOL and Monofocal Toric IOL have been distributed globally since 2005.

As can be seen in Figure 2, the profile of the ReSTOR Toric IOL is identical to that of other single-piece IOLs in the AcrySof family. The raw materials and manufacturing methods are the same as those used with the previously qualified AcrySof IOL models. Like the parent multifocal IOL, the apodized diffractive multifocal optic is on the anterior surface of the lens. The toric component is incorporated on the posterior surface, which is the same as the monofocal toric IOL. The anterior surface of the ReSTOR Toric IOL is also designed with negative spherical aberration to compensate for the positive spherical aberration of the cornea, similar to other AcrySof aspheric lenses that are currently commercially available. The optical portion of the IOL is biconvex and consists of a soft acrylic AcrySof material capable of being folded prior to implantation, allowing placement through an incision smaller than the optic diameter of the lens. After surgical implantation into the eye, the lens unfolds and returns to its original shape.

Figure 2. AcrySof Family of Single-piece IOLs



AcrySof Single-Piece Monofocal IOL | AcrySof Monofocal Toric IOL | AcrySof ReSTOR Multifocal IOL | AcrySof ReSTOR Toric IOL

Preclinical testing followed FDA guidance and met current standards for chemical characterization, optical testing, mechanical testing, and ethylene oxide sterilization.

The ReSTOR Toric IOL will be available in 4 models (SND1T3, SND1T4, SND1T5, and SND1T6) to provide 4 different cylinder powers and astigmatic correction ranges (Table 1) and are available in spherical equivalent powers from +6 D to +30 D in 0.5 D steps.

Table 1. ReSTOR Toric IOL Models, Cylinder Power and Corneal Astigmatism Correction Range

	Cylinder Power		**Recommended Corneal Astigmatism Correction Range**	
Lens Model	IOL Plane	Corneal Plane[a]	Lower	Upper
SND1T3	1.50	1.03	0.75	1.28
SND1T4	2.25	1.55	1.29	1.80
SND1T5	3.00	2.06	1.81	2.32
SND1T6	3.75	2.57	2.33	2.82

[a] Based on an average pseudophakic human eye

1.3 DESIGN OF CLINICAL STUDY C-09-036

Clinical Study C-09-036 was a prospective, nonrandomized, unmasked, parallel-group study designed for bilateral implantation of a minimum of 510 (maximum of 600 subjects) subjects in total, with a minimum of 340 subjects implanted with the investigational ACRYSOF IQ ReSTOR Multifocal Toric IOL Model SND1T3-SND1T6, and a minimum of 170 subjects implanted with the FDA approved ACRYSOF ReSTOR Multifocal IOL Model SA60D3 (Control IOL), at up to 25 investigational sites in the United States. The

study design and endpoints followed the recommendations in the applicable US and international standards for development of multifocal and toric lenses (ANSI-Z80.12, ANSI-Z80.30, ISO 14155, ISO 11979-7 and ISO 11979-9). Clinical Study C-09-036 intended to show that the addition of a toric surface to the multifocal lens would offer patients with astigmatism similar effectiveness and safety outcomes as those expected with a multifocal lens in patients with minimal to no astigmatism. As a result, safety and effectiveness in subjects with corneal astigmatism (0.75 D to 2.82 D) treated with the investigational ReSTOR Toric IOL were compared to subjects with minimal to no corneal astigmatism (< 0.75 D) treated with the parent (Control) IOL. Other than the level of pre-existing astigmatism, subjects receiving both the ReSTOR Toric IOL and the Control IOL met the same inclusion and exclusion criteria. A total of 574 subjects were implanted with an IOL in the study (386 with ReSTOR Toric IOL and 188 with the Control IOL) at 23 sites in the US.

The primary effectiveness objective in Clinical Study C-09-036 was to estimate the difference in the first implanted eye in visual acuity outcomes between the ReSTOR Toric IOL and the Control IOL at 12 months (Visit 5A), and to demonstrate that the difference is less than a prespecified clinical performance target. The key effectiveness endpoints were monocular uncorrected distance visual acuity (UCDVA) and uncorrected near visual acuity (UCNVA) at fixed distance. The clinical performance target was 0.1 logMAR unit in the first implanted eye. Additional effectiveness endpoints consisted of binocular near, intermediate and distance visual acuity, reduction of cylinder, IOL rotation and misalignment, increased spectacle independence as measured by Item 1 of *the Spectacle Independence Lens Vision Evaluation and Repurchase* (SILVER) questionnaire ("How often do you wear eyeglasses or contact lenses overall"?), and contrast sensitivity.

The primary safety objective was to estimate the rate of actual and potential secondary surgical interventions (SSIs) related to optical properties of the IOL for first and second operative eyes separately at 12 months after the second eye surgery (Visit 5). If the SSI was related to optical properties, each event was then categorized as an *actual SSI*, if an SSI was performed, or *potential SSI,* if an SSI was warranted but was not performed.

The secondary safety objective included analysis of the rate of severe visual disturbances/distortions associated with cataract extraction and IOL implantation, including glare, halos, and starbursts based upon the findings from *The Assessment of Photic Phenomena and Lens Effects* (APPLES) questionnaire, which is a Patient Reported Outcome (PRO) instrument. Other supportive safety endpoints included adverse events (AEs), device deficiencies, surgical problems, subjective posterior capsule opacification (PCO), and posterior capsulotomy.

1.4 EFFECTIVENESS OF RESTOR TORIC IOL IN CLINICAL STUDY C-09-036

The ReSTOR Toric IOL is effective in providing, near, intermediate and distance vision, correction of preexisting corneal astigmatism, and increased spectacle independence, as demonstrated by the data from Clinical Study C-09-036.

- The ReSTOR Toric IOL met all key effectiveness endpoints:
  - UCDVA in the first implanted eye was 0.126 logMAR for the ReSTOR Toric IOL and 0.125 logMAR for the Control IOL with a difference of 0.001 and upper 95% CI of 0.030, meeting the prespecified clinical performance target of 0.1 logMAR. The analysis of UCDVA in the second eye also met the clinical performance target.
  - UCNVA at fixed distance (40 cm for the ReSTOR Toric IOL and 33 cm for the Control IOL) in the first implanted eye was 0.193 logMAR for the ReSTOR Toric IOL and 0.236 logMAR for the Control IOL, with a difference of -0.044, and an upper 95% CI of -0.017 meeting the prespecified clinical performance target of 0.1 logMAR. The analysis of UCNVA in the second eye also met the clinical performance target.
- Mean binocular uncorrected intermediate visual acuity results demonstrated clinically relevant differences favoring the ReSTOR Toric IOL at 50 cm (0.13 logMAR for the ReSTOR Toric and 0.28 logMAR for the Control), 60 cm (0.17 logMAR for the ReSTOR Toric and 0.32 for the Control), and 70 cm (0.21 logMAR for the ReSTOR Toric and 0.32 for the Control).
- The ReSTOR Toric IOL provided combined near, intermediate, and distance vision of 20/40 or better in 92.2% of subjects.
- The ReSTOR Toric IOL effectively reduced cylinder in the range of 0.75 D to 2.82 D:
  - Postoperatively, 94.1% of subjects achieved a reduction in astigmatism to within 1.0 D of the targeted cylinder, and 74.5% achieved a reduction to within 0.5 D of the targeted cylinder in the first eye.
  - In the second eye, 97.6% of subjects achieved a reduction to within 1.0 D of target cylinder and 79.5% achieved a reduction to within a 0.5 D of target cylinder.
- Accuracy of lens placement was demonstrated for the ReSTOR Toric IOL with the mean absolute misalignment at surgery being 5.0° ± 6.1° in the first operative eyes (difference between intended axis orientation calculated preoperatively, and achieved axis orientation - measured at the time of surgery).
- At the 12 month visit, 97.2% of first and second eyes had no more than 10 degrees of rotation (difference between the IOL axis at the surgery visit and at a subsequent visit).
- The mean absolute IOL rotation at the 12 month visit was 2.7° ± 5.8° in the first operative eyes and 2.2° ± 2.7° in the second operative eyes.
- In subjects treated with the ReSTOR Toric IOL, 75.7% achieved increased spectacle independence as measured by Item 1 of the SILVER patient reported outcomes questionnaire

("How often do you wear eyeglasses or contact lenses overall"?) at 12 months compared to 69.4% treated with the Control IOL.

- In subjects treated with the ReSTOR Toric IOL, 72.5% and 94.6% of subjects did not use spectacles or contacts for up close and distance vision respectively, compared to 70.0% and 92.8% of subjects with the Control IOL.
- Supportive and sensitivity analyses were consistent with findings from pre-specified primary effectiveness analyses. For UCDVA, more than 90% of subjects in both treatment groups achieved 20/40 Snellen visual acuity or greater in both eyes. For UCNVA at fixed distance, more than 80% in both treatment groups achieved 20/40 Snellen visual acuity or greater in both eyes.
- In the ReSTOR Toric IOL group, 91% of subjects reported that they would choose to have the same lens model implanted again, and a similar percentage was observed in the Control IOL group (90%).

1.5 SAFETY FINDINGS IN CLINICAL STUDY C-09-036

Overall, as demonstrated by the data from Clinical Study C-09-036, no unanticipated safety concerns were identified with the ReSTOR Toric IOL. Based on safety parameters collected in this clinical study, the safety profiles observed for the ReSTOR Toric IOL and the Control IOL were generally similar.

- The rate of actual or potential SSIs due to the optical properties for the ReSTOR Toric IOL was 1.04% in the first eyes (0.52% in the second eyes) with a similar rate to subjects implanted with the Control IOL. *Note:* no formal hypothesis test was conducted on the primary safety endpoint.
- Overall, the rate of severe visual disturbances/distortions at 12 months (Visit 5) was similar in subjects implanted with the ReSTOR Toric IOL relative to subjects implanted with the Control IOL.
- Although the overall SSI rate for the ReSTOR Toric IOL (first and second eyes) exceeded the Safety and Performance Endpoint (SPE) rate provided in the ISO guidance, a majority of the events were not related to the IOL according to the investigator or a Sponsor assessment. The SSI rate for the second eyes of the Control IOL also exceeded the SPE grid rate.
- The rate of eyes experiencing any ocular adverse device effects (ADEs) was less than 1% in the ReSTOR Toric IOL group.
- The types of all ocular AEs reported were similar between the ReSTOR Toric IOL and Control IOL groups.
- Of the 5 subjects who discontinued from the study due to an adverse event, none of these non-ocular events were related to the surgical procedure or the IOL.
- Device deficiencies were infrequent during the study.
- The capsulorhexis tears and anterior radial tears occurred infrequently in both groups with good postoperative visual outcomes for these subjects.

- No greater incidence of PCO or the need for YAG laser posterior capsulotomy was observed in the ReSTOR Toric IOL group when compared to the Control IOL group.

1.6 BENEFIT RISK DISCUSSION

In the US, more than 3 million cataract surgeries are performed each year. However, the subset of patients who have cataract concomitant with corneal astigmatism have limited options for an IOL that can correct astigmatism and provide near, intermediate, and distance vision. Alcon developed the ReSTOR Toric IOL by combining two clinically studied, FDA approved and globally marketed IOL technologies (multifocal and toric) in a single lens. The parent IOLs both have well established safety and effectiveness profiles.

After conducting preclinical testing that met applicable standards, industry and FDA guidelines, Alcon proceeded with the design of the clinical study. The design of Clinical Study C-09-036 incorporated feedback received during interaction with the FDA on certain aspects of the study such as visual acuity, contrast sensitivity, increased spectacle independence, rate of visual disturbances/distortion, and the rate of secondary surgical interventions (SSIs) due to optical properties. Clinical Study C-09-036 was a non-randomized, unmasked, parallel-group, prospective trial that compared the safety and effectiveness in subjects with corneal astigmatism (0.75 D to 2.82 D) treated with the ReSTOR Toric IOL to subjects with minimal to no corneal astigmatism (< 0.75 D) treated with ReSTOR multifocal IOL (Control IOL). Although the two study populations had different levels of preoperative astigmatism, implantation of the appropriately selected IOL resulted in similar near and distance visual acuity and contrast sensitivity outcomes between the two populations.

Clinical Study C-09-036 demonstrated that the ReSTOR Toric IOL provides patients with the benefits of astigmatism correction as well as near, intermediate and distance vision, and increased spectacle independence, with no unanticipated safety concerns identified in the study for the ReSTOR Toric IOL.

The ReSTOR Toric IOL demonstrated UCDVA and UCNVA (at fixed distance) that were non-inferior to the Control IOL. In addition, the ReSTOR Toric IOL demonstrated combined near, intermediate, and distance vision of 20/40 or better in 92.2% of subjects, correction of pre-operative corneal astigmatism (74.5% of subjects within 0.5 D and 94.1% of subjects within 1.0 D of target), and increased spectacle independence for a high percentage of subjects (75.7%).

Clinical Study C-09-036 also demonstrated that there were no unanticipated risks when combining multifocal and toric corrections relative to the risks associated with the implantation of the Control IOL.

- The rates of actual and potential secondary surgical interventions due to optical properties, as well as the rates of severe visual disturbances, were comparable between the ReSTOR Toric IOL and Control IOL.
- There were also no clinically relevant differences in contrast sensitivity.

In addition to the confirmatory Clinical Study C-09-036, the ReSTOR Toric IOL has been evaluated in four clinical studies conducted outside of the United States. Results from these studies were consistent with the results of Clinical Study C-09-036 with respect to the safety and effectiveness (benefit to risk ratio) of the ReSTOR Toric IOL.

- Although there was a higher rate of IOL misalignment (intended IOL axis orientation compared with the axis orientation observed at postoperative visits) compared to that observed in Clinical Study C-09-036, the difference was most likely due to a difference in IOL axis assessment between the studies, rather than a reflection of the differences in the study populations or lens performance.
- Few subjects required surgical intervention for realignment or had poor visual outcomes, and the overall safety experience including SSIs due to optical properties and visual distortions/disturbances were consistent with the experience in the US.

The postmarket experience with the ReSTOR Toric IOL has also been favorable. The AEs reported from postmarketing experience from outside of the US (over 93,000 units sold since 2010) are similar to those observed during clinical development and are generally consistent with known complications associated with cataract surgery following the implantation of a Toric or Multifocal IOL.

Overall, the ReSTOR Toric IOL provides the combined benefits of astigmatism correction, near, intermediate and distance vision, and increased spectacle independence to astigmatic cataract patients with no unanticipated risks. This favorable benefit to risk ratio supports that the ReSTOR Toric IOL is safe and effective when implanted according to the directions for use.

2 BACKGROUND INFORMATION

2.1 TREATMENT OF APHAKIA AND ASTIGMATISM

Overall, 17.1% of the US population has a cataract (Friedman 2012) with the prevalence slightly greater in females and increasing with age. In ages 65-69, 24.7% of the population has a cataract. Diagnosis of cataract has increased significantly over the last decade, and cataract surgery is now one of the most common surgical procedures performed in the US.

Phacoemulsification, in which the cataractous lens is emulsified and extracted using ultrasound and aspiration, is the most common method for cataract lens removal in the US. Cataractous lens removal is typically followed by implantation of a posterior chamber IOL within the capsular bag during the same surgery. Implantation of an IOL is necessary to correct the refractive error due to aphakia, or absence of the lens of the eye after the cataractous lens is removed.

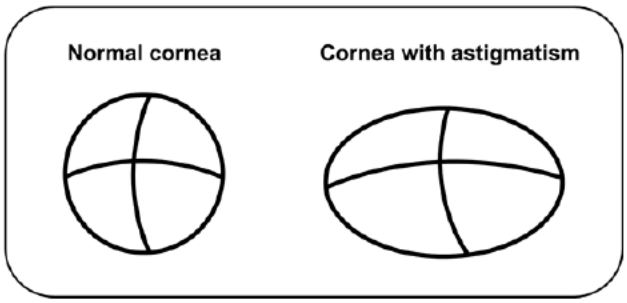
Ophthalmological co-morbidity with cataracts is highly prevalent and can influence the type of IOL selected to treat aphakia. Myopia, or nearsightedness, causes reduced visual acuity for distance vision, and hyperopia, or farsightedness, causes reduced visual acuity for distance and near vision. Presbyopia typically presents with decreased visual acuity for intermediate and near vision. In addition to these conditions, many patients in the US also have astigmatism, further influencing the type of IOL selected.

2.1.1 Description of Astigmatism

Astigmatism is a variation in the shape or curvature of the cornea, the crystalline lens (lenticular astigmatism) or a combination of both. Normally, the cornea and crystalline lens are smooth and curved equally in all directions (like a basketball), helping to focus light rays sharply onto the retina. When the cornea or lens is not evenly curved (like a football), light rays are not refracted properly on the retina, causing a refractive error. This irregular or toric shape of the cornea is called corneal astigmatism. When the shape of the crystalline lens is distorted, it is called lenticular astigmatism. If left untreated, astigmatism can and will cause blurred vision at all distances.

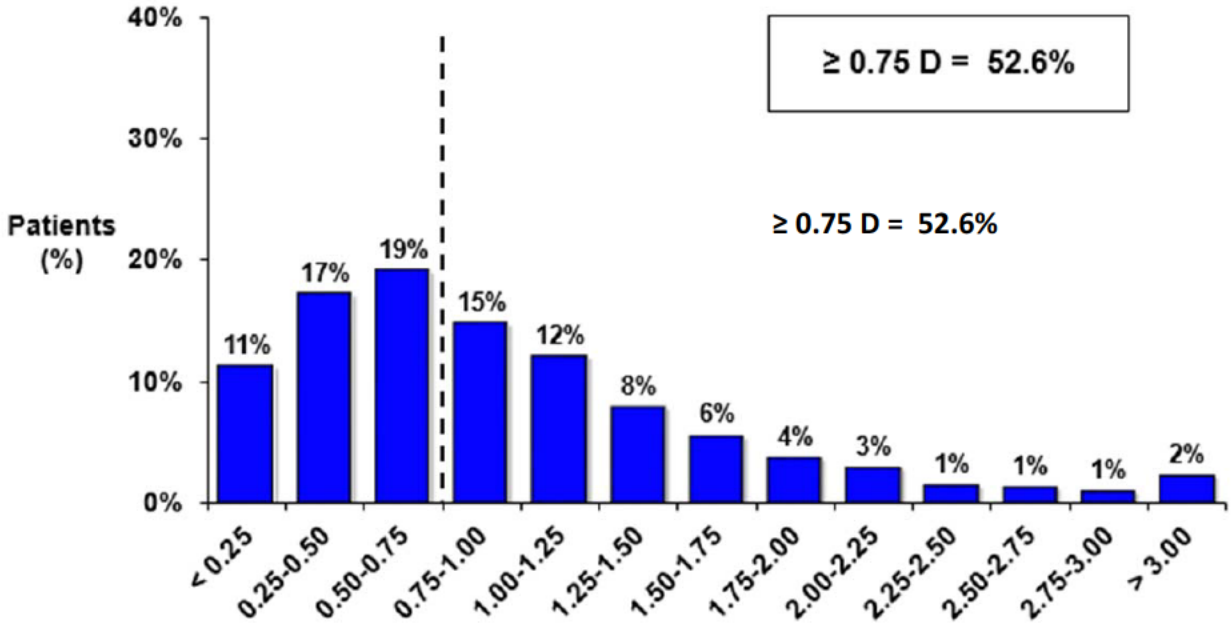
Anterior corneal astigmatism refers to the toricity of the anterior corneal surface. The astigmatic or toric principal meridian of maximum curvature is the steep meridian and the orthogonal principal meridian of minimal curvature is called the flat meridian. The powers of the two principal meridians are expressed in diopters (D). The difference between the powers of the two principal meridians (steep and flat) provides the magnitude of astigmatism. The difference between a normal cornea and one with astigmatism is illustrated in Figure 3.

Figure 3. Comparison Between a Normal Cornea and a Cornea with Astigmatism



A recent study showed that more than 50% of the US population has corneal astigmatism of 0.75 D or greater prior to cataract surgery[1]. The breakdown of corneal astigmatism in 0.25 D increments is shown in Figure 4.

Figure 4. Prevalence of Corneal Astigmatism Prior to Cataract Surgery



[1] N=6,000. Copyright 2013, Warren E. Hill, MD; keratometry database; adapted with permission

2.1.2 Treatment of Aphakia and Astigmatism

In order to provide clear vision at near, intermediate and distance, an ophthalmologist must correct for spherical power errors (myopia or hyperopia), cylindrical power errors (astigmatism), and presbyopia when present. A patient who has spherical error, astigmatism, and presbyopia with their natural lens (i.e. does not have a cataract), is typically corrected with glasses or contact lenses. This is necessary to provide clear vision for near and distance. Otherwise, patients would have blurred vision at all distances in some regard.

Similarly, when treating cataract patients, an ophthalmologist must correct aphakia, spherical power errors, cylindrical power errors, and presbyopia as applicable. This is absolutely necessary to provide near and distance vision for patients with less dependence on spectacles.

Currently, several types of IOLs are used to treat aphakia:

- ***Monofocal*** IOLs have one focal point targeted for the spherical equivalent to provide patients their clearest vision at one distance only. Since a monofocal lens corrects for spherical errors only, astigmatism and presbyopia will not be addressed, resulting in blurry vision due to the uncorrected astigmatism. As a result, patients with > 0.75 D of astigmatism that undergo cataract surgery will typically still need corrective lenses (spectacles or contact lenses) or other surgical procedures to improve their near and distance vision.
- ***Multifocal*** IOLs are designed with refractive and/or diffractive optical properties, which work by dividing light into multiple focal points that provide patients with simultaneous near, intermediate, and distance vision (Avitabile 2001, Leyland 2003, Bellucci 2005, Davison 2006, Lane 2006b, Bi 2008, Blaylock 2008, De Vries 2008, Alfonso 2009). Patients who have been implanted with multifocal IOLs have improved vision at near and intermediate distances when compared to conventional monofocal IOLs and may achieve increased spectacle independence (Javitt 2000, Chiam 2006, Kohnen 2006, Souza 2006, Vingolo 2007, Alfonso 2009). However, in the United States, multifocal IOLs do not correct corneal astigmatism and are not indicated in patients with more than 1.0 D of corneal astigmatism.
- ***Monofocal Toric*** IOLs correct aphakia and corneal astigmatism (Horn 2007, Bauer 2008). Like other monofocal IOLs, monofocal Toric IOLs have one focal point targeted for the spherical equivalent to provide patients their clearest vision at one distance only. As a result, presbyopia is left unaddressed and spectacle use is typically still necessary for seeing up close.

More than 50% of the patients who undergo cataract surgery have corneal astigmatism ≥ 0.75 D, which may significantly limit an optimal visual outcome if left uncorrected (Riley 2001, Ferrer-Blasco 2009). An astigmatic patient's vision is typically not completely corrected with any of these options and, therefore, additional correction will be needed. Astigmatic patients receiving a monofocal, multifocal, or monofocal toric IOL could be corrected with glasses or contact lenses, or might undergo a secondary

surgical procedure to be less dependent on their glasses after their cataract surgery. Manual limbal or corneal relaxing incisions and femtosecond astigmatic keratotomy are treatments for the correction of astigmatism that may be performed at the time of cataract surgery. While both of these procedures are advantageous because they can conveniently be performed at the time of cataract surgery, their effectiveness has not been demonstrated in a large confirmatory clinical study. In addition, these procedures have not been approved for the indication of astigmatism correction in the United States.

Excimer laser refractive procedures, such as LASIK or photorefractive keratectomy, are more accurate but more costly to the patient. They also require the treatment of astigmatism to be staged, typically one to three months after they have healed after cataract surgery, which can cause frustration for the patients as they wait for their vision to improve. Managing temporary blurred vision from uncorrected astigmatism after cataract surgery presents a dilemma because the patients may need to purchase a temporary pair of glasses, resulting in an additional cost to the patient.

These options for secondary surgical astigmatic correction may pose risks to the patient such as corneal perforation, the chance for infection, or compromise to the ocular surface.

The images in Figure 5 (below) simulate what a patient with 1.0 D of corneal astigmatism might experience should they receive the ReSTOR Toric IOL as compared to a monofocal, multifocal, or monofocal toric IOL. As illustrated in the figure, an astigmatic patient's vision is typically not completely corrected with any of these options and, therefore, additional correction will be needed. For Patients who are seeking to be less dependent on their glasses after cataract surgery and desire a single multifocal intraocular lens that can correct for spherical error, astigmatism, and near vision (i.e. presbyopia) without the need for additional surgical procedures, a multifocal toric IOL such as the ReSTOR Toric IOL would provide patients in the US an option to correct presbyopia and astigmatism with one IOL in a single surgical procedure.

Figure 5. Simulation of Visual Outcomes with a Monofocal, Monofocal Toric, Multifocal, and ReSTOR Toric IOL in a Patient with 1.0 D of Astigmatism

	Near	Intermediate	Distance
Monofocal IOL (with 1.0 D of Astigmatism)			
Monofocal Toric IOL (with 1.0 D of Astigmatism)			
Multifocal IOL (with 1.0 D of Astigmatism)			
ReSTOR Toric IOL (with 1.0 D of Astigmatism			

2.2 OVERVIEW OF THE RESTOR TORIC IOL

2.2.1 AcrySof Family of Intraocular Lenses

The AcrySof Family of Intraocular Lenses, which includes the ReSTOR Toric IOL, was initially approved in the United States in 1994. Over 75 million IOLs with the AcrySof material have been implanted in patients in over 100 countries around the world. The AcrySof single-piece platform was first approved in the US as a monofocal IOL in 1999. Since that time, the AcrySof family has expanded with the addition of features that include a blue-light blocking chromophore, aspheric correction, astigmatic correction, and multifocality, which are all based on the original AcrySof single-piece IOL.

All IOLs in the AcrySof family share several basic features. The AcrySof material is a high refractive index soft acrylic material which is capable of being folded prior to implantation, allowing placement through an incision smaller than the optic diameter of the lens. The lens is biconvex and both the optical and haptic portions of IOLs utilizing the single-piece design are made of the AcrySof material. The original AcrySof material provides standard ultraviolet (UV) absorption and gives IOLs made of this material a clear appearance. The addition of a proprietary blue light filtering chromophore, which filters light in a manner that approximates the human crystalline lens in the 400-475 nm blue light wavelength range

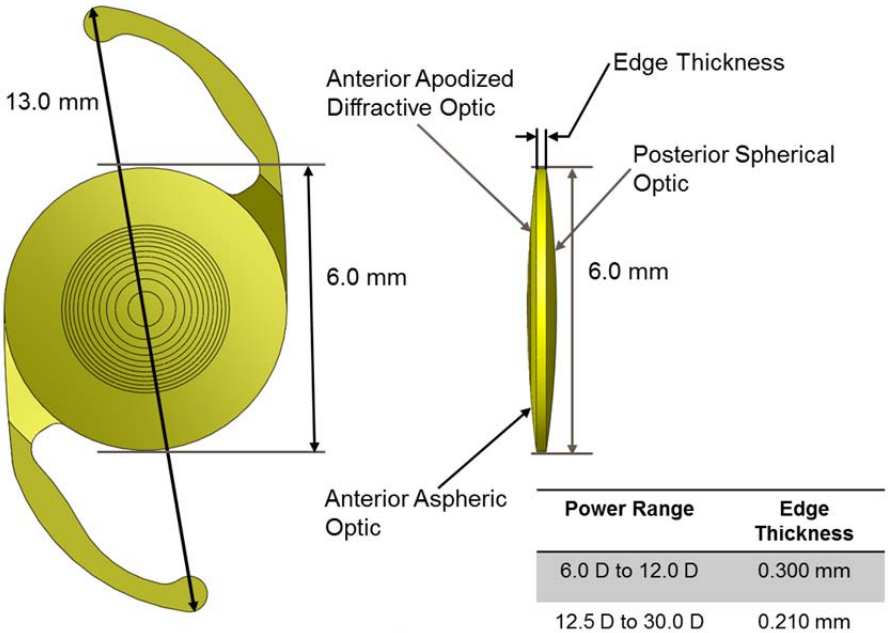
(Boettner and Wolter, 1962) reduces transmittance of short wavelength blue light and gives IOLs with this chromophore a yellow color.

The AcrySof ReSTOR Multifocal IOL was initially approved in the US in 2005 under PMA P040020. The originally approved model, Model SA60D3, was a non-aspheric, clear IOL with a +4.0 D add power which is the same model that was utilized as the control in Clinical Study C-09-036. Since the original approval, additional approvals have been received to add the following features: blue-light blocking chromophore, aspheric correction, and a +3.0 D add power. All IOLs in the ReSTOR family have the same indication:

> *The AcrySof® ReSTOR® Apodized Diffractive Posterior Chamber Intraocular Lens (IOL) is intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. The lens is intended to be placed in the capsular bag.*

The current design of the AcrySof ReSTOR Multifocal IOL is depicted in Figure 6. The only differences between this depiction and the originally approved model are the presence of two features: aspheric anterior surface and the blue-light filtering chromophore. Both the +4.0 D add-power and the +3.0 D add-power ReSTOR IOLs are clinically studied and globally approved. Approximately 1.6 million ReSTOR IOLs have been implanted since their introduction to the market.

Figure 6. AcrySof ReSTOR Multifocal IOL



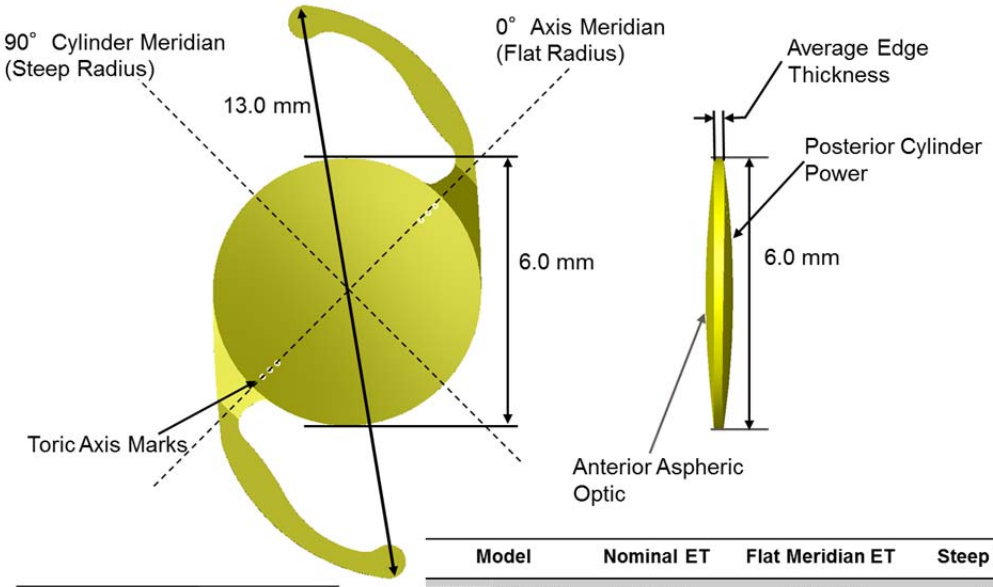
Power Range	Edge Thickness
6.0 D to 12.0 D	0.300 mm
12.5 D to 30.0 D	0.210 mm

The AcrySof monofocal Toric IOL was also initially approved in the US in 2005 under PMA P930014 (Supplement S015). The originally approved models, Models SA6AT3, SA6AT4, and SA6AT5, were non-aspheric, clear IOLS that were clinically studied prior to approval. Since the original approval, additional approvals have been received to add the following features: blue-light blocking chromophore, aspheric correction, and additional astigmatic correction (Models SN6AT6, SN6AT7, SN6AT8, and SN6AT9). All AcrySof Monofocal Toric IOLs have the same indication:

> *The AcrySof® IQ Toric posterior chamber intraocular lenses are intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and pre-existing corneal astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia, who desire improved uncorrected distance vision, reduction of residual refractive cylinder and increased spectacle independence for distance vision.*

AcrySof monofocal Toric IOLs are globally approved and approximately 2 million monofocal Toric IOLs have been implanted since their introduction to the market. The current design of the AcrySof monofocal Toric IOL is depicted in Figure 7.

Figure 7. AcrySof Monofocal Toric IOL



Power Range	Average Edge Thickness
6.0 D to 12.0 D	0.30 mm
12.5 D to 34.0 D	0.21 mm

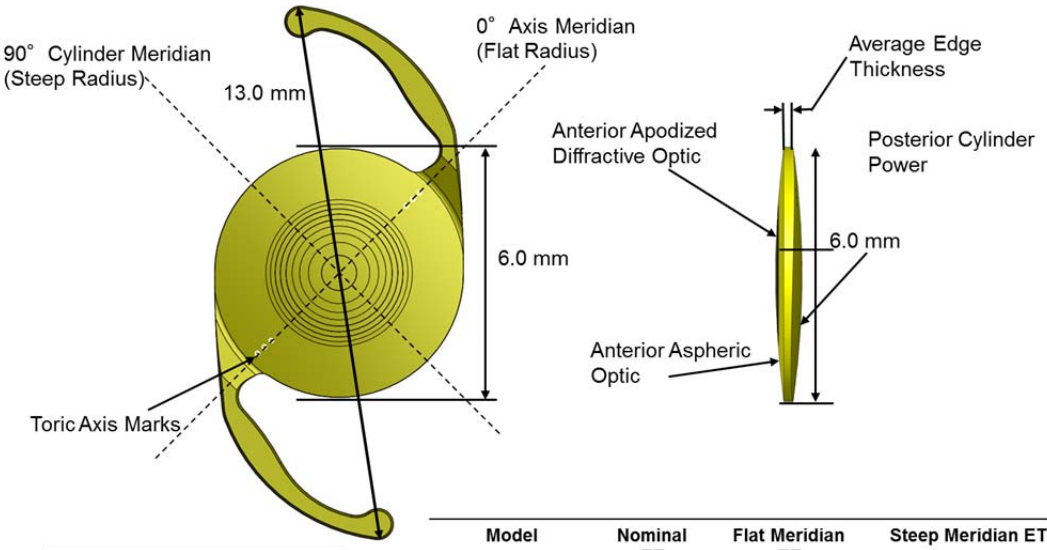
Model	Nominal ET	Flat Meridian ET	Steep Meridian ET
SN6AT3-21.0D	0.21 mm	0.226 mm	0.194 mm
SN6AT4-21.0D	0.21 mm	0.234 mm	0.186 mm
SN6AT5-21.0D	0.21 mm	0.242 mm	0.179 mm
SN6AT6-21.0D	0.21 mm	0.250 mm	0.170 mm

4

2.2.2 Description of the ReSTOR Toric IOL

To provide an option for patients who require astigmatic correction but who also desire near, intermediate, and distance vision, and a decreased need for spectacles, Alcon incorporated the toric design of the existing AcrySof monofocal Toric IOL on the posterior surface of the existing ReSTOR multifocal lens platform. The combination of multifocality and astigmatic correction in the ReSTOR Toric IOL is intended to provide astigmatic cataract patients with near, intermediate, and distance vision, as well as to correct pre-existing corneal astigmatism. The anterior surface is designed with -0.1 µm (micron) of negative spherical aberration to compensate for the positive spherical aberration of the cornea. The design of the ReSTOR Toric IOL is depicted in Figure 8 and the physical characteristics are summarized in Table 2.

Figure 8. AcrySof ReSTOR Toric IOL



Power Range	Average Edge Thickness
6.0 D to 12.0 D	0.30 mm
12.5 D to 30.0 D	0.21 mm

Model	Nominal ET	Flat Meridian ET	Steep Meridian ET
SND1T3-21.0D	0.21 mm	0.226 mm	0.195 mm
SND1T4-21.0D	0.21 mm	0.234 mm	0.187 mm
SND1T5-21.0D	0.21 mm	0.242 mm	0.179 mm
SND1T6-21.0D	0.21 mm	0.249 mm	0.171 mm

Table 2. Physical Characteristics of the ReSTOR Toric IOL

Optic Type	Biconvex Apodized Diffractive Aspheric Toric
Optics/Haptics Material	Ultraviolet/blue light filtering Acrylate/Methacrylate Copolymer
Index Of Refraction	1.55
Optic Powers (spherical equivalent diopters)	6.0 D to 30.0 D
Haptic Configuration	STABLEFORCE®
Optics/Haptic Color	Yellow
Optic Diameter (mm)	6.0
Overall Length (mm)	13.0
Haptic Angle	0º

The surgical procedure to implant the ReSTOR Toric IOL is identical to that used to implant other IOLs. Following removal of the cataractous lens, the foldable IOL is placed into the eye with an injector in a conventional manner. The lens gently unfolds inside the eye, and the haptics expand. Residual ophthalmic viscosurgical device (OVD) is removed from behind the lens, and the lens is centered. The IOL is then aligned in the same manner as other toric IOLs. The flat meridian of the IOL is identified with the indentations in the form of dots on the posterior surface of the optic. The dotted indentations on the IOL are then aligned with the recommended axis of placement determined by the ReSTOR Toric calculator.

The ReSTOR Toric IOL will be available in 4 different cylinder powers (1.50 D, 2.25 D, 3.00 D, and 3.75 D) and in spherical equivalent powers of +6 D to +30 D. Table 3 summarizes the model numbers and corneal astigmatism correction ranges.

Table 3. ReSTOR Toric IOL Models, Cylinder Power and Corneal Astigmatism Correction Range

	Cylinder Power		**Recommended Corneal Astigmatism Correction Range**	
Lens Model	IOL Plane	Corneal Plane[a]	Lower	Upper
SND1T3	1.50	1.03	0.75	1.28
SND1T4	2.25	1.55	1.29	1.80
SND1T5	3.00	2.06	1.81	2.32
SND1T6	3.75	2.57	2.33	2.82

[a] Based on an average pseudophakic human eye

2.2.3 Preclinical Testing

The ReSTOR Toric IOL is made of the same raw material and manufacturing materials used with the previously approved AcrySof IOL models. Preclinical testing followed FDA guidance with all testing meeting current standards for chemical characterization, optical testing, mechanical testing, and ethylene oxide sterilization.

Summaries of the studies performed with AcrySof raw material and previously qualified AcrySof IOLs are provided in Table 4 through Table 6. In addition to the studies summarized below, the ethylene oxide sterilization cycle was validated and assures a minimum Sterility Assurance Level of 10^{-6}.

Table 4. Preclinical Biocompatibility Testing

Test	Result
Genotoxicity	
Ames Test	Non-mutagenic
Chromosome Aberration Assay	Non-clastogenic
Mouse Lymphoma Forward Mutation Assay	Non-mutagenic
Cytotoxicity –	
Agarose Overlay (Direct)	Non-cytotoxic
MEM Elution	Non-cytotoxic
V79 Colony Inhibition Assay (Extract)	No cell growth inhibition or cytotoxicity
V79 Colony Inhibition Assay (Direct)	No cell growth inhibition or cytotoxicity
Nd:YAG Laser Exposure Test (Extract)	Non-cytotoxic
Muscle Implantation – 7, 30 days	No significant biological responses
Sensitization – Guinea Pig Maximization	Non-sensitizing
Implantation – Ocular Implantation (6-Month)	No evidence of irritation

Table 5. Preclinical Chemical Compatibility Testing

Test	Result
Material Stability – aging and leachability	Passed
Material Extraction	Passed
Process Extractable Analysis	Passed
Heavy Metal Analysis	Passed
Fourier Transform/Infrared Spectroscopy	Passed
Contact Angle	Passed
X-ray photoelectron Spectroscopy	Passed

Table 6. Preclinical Optical and Mechanical Testing

Test	Result
Haptic Compression Force	Passed
Haptic Compression Force Decay	Passed
Axial Displacement	Passed
Optic Decentration	Passed
Optic Tilt	Passed
Angle of Contact	Passed
Fatigue Testing	Passed
Haptic Strength	Passed
Spectral Transmittance	Passed
Modulation Transfer Function	Passed
Optical Evaluation after Multiple Folds	Passed
Test Photostability	Passed
Nd: YAG Laser Exposure Test	Passed
Refractive Index	Passed

2.2.4 ReSTOR Toric IOL Calculator

The ReSTOR Toric IOL web-based calculator (www.acrysoftoriccalculator.com) is a validated software tool designed to assist the surgeon with estimating the power and cylinder of the IOL that should be used for the patient. Additionally, the calculator assists the surgeon in selecting the correct ReSTOR Toric IOL model based upon the appropriate cylinder and keratometry measurements. Software validation was performed for the ReSTOR Toric IOL calculator according to the procedures described in FDA's "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices". Figure 9 and Figure 10 show screen shots of the ReSTOR Toric calculator and example of calculator outputs, respectively.

The ReSTOR Toric IOL Calculator is very similar to the previously approved calculator which is currently used for Alcon's Toric Monofocal IOLs. The selection criteria for the cylinder power of the lens used in the previously approved AcrySof Monofocal Toric IOL calculator generally targets under correction of corneal astigmatism; whereas, the cylinder power of the lens selected by ReSTOR Toric calculator has a cylinder power at the corneal plane that is within approximately ±0.25 diopter of the crossed-cylinder result. The IOL selection criteria of the ReSTOR Toric calculator minimize the magnitude of anticipated residual cylinder.

Figure 9. ReSTOR Toric Web Calculator

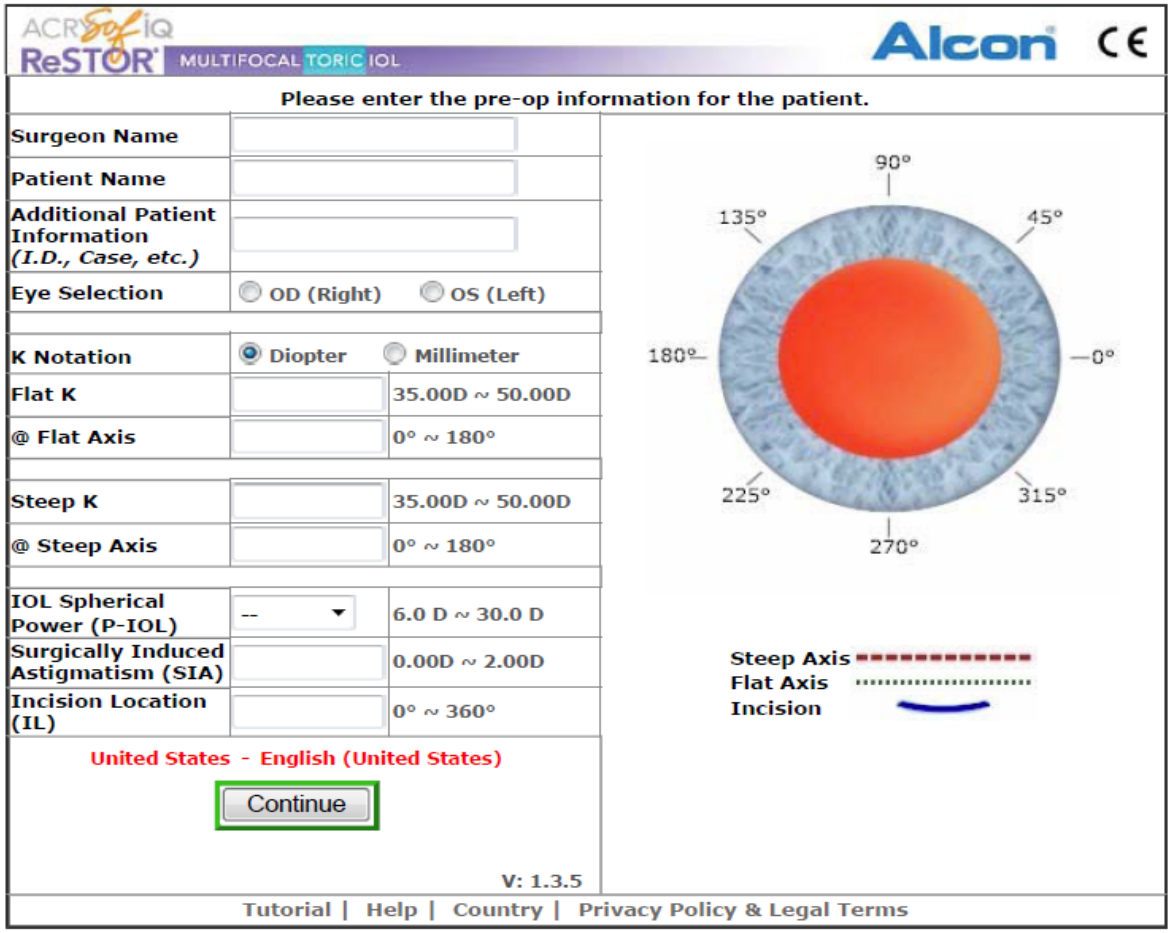
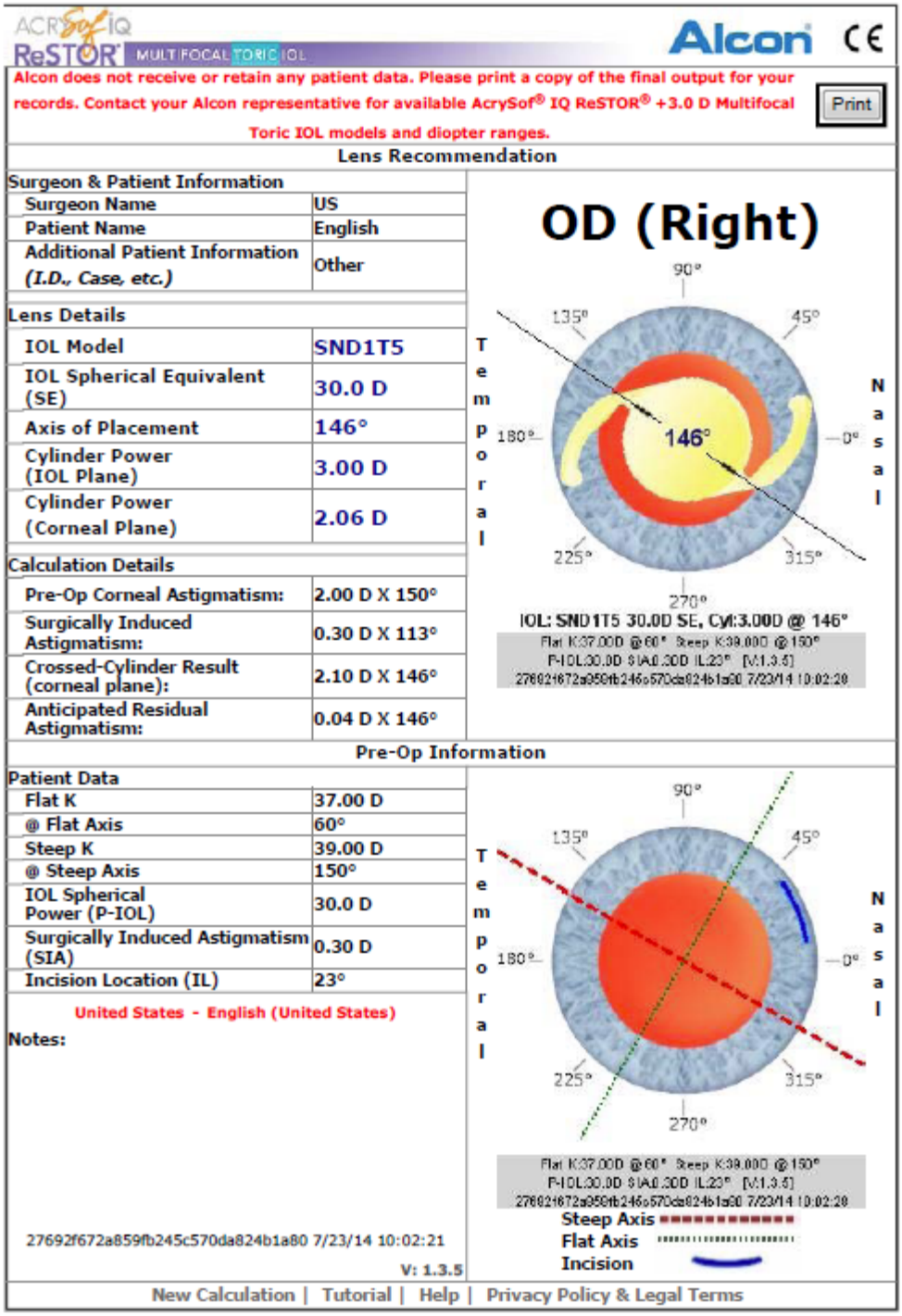


Figure 10. ReSTOR Toric Calculator Results



2.3 REGULATORY HISTORY

As stated above, the ReSTOR Toric IOL was developed using the same AcrySof material and AcrySof single-piece design as the AcrySof ReSTOR Multifocal (PMA P040020) and AcrySof Toric (P930014/S015 and S045) parent IOLs. AcrySof ReSTOR Multifocal and AcrySof Toric IOLs have been distributed globally since 2005.

The indication for the ReSTOR Toric IOL is consistent with the approved indication for other ReSTOR Multifocal IOLs with the only differences being related to the addition of the toric component. The verbiage added to the ReSTOR Toric IOL regarding the toric component is identical to the language used in the currently approved indication for Alcon's monofocal Toric IOL. A comparison of the ReSTOR indication, the Monofocal Toric indication, and the ReSTOR Toric indication is shown below with the added toric language highlighted in **blue** text:

ReSTOR Multifocal IOL	Monofocal Toric IOL	ReSTOR Toric IOL
Indications for Use: The AcrySof® ReSTOR® Apodized Diffractive Posterior Chamber Intraocular Lens (IOL) is intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. The lens is intended to be placed in the capsular bag.	Indications for Use: The AcrySof® IQ Toric posterior chamber intraocular lenses are intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and pre-existing corneal astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia, who desire improved uncorrected distance vision, reduction of residual refractive cylinder and increased spectacle independence for distance vision.	Indications for Use: The AcrySof® IQ ReSTOR® Multifocal Toric Posterior Chamber Intraocular Lens (IOL) are intended for primary implantation for the visual correction of aphakia **and pre-existing astigmatism** secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision, **reduction of residual refractive cylinder** and increased spectacle independence. The lens is intended to be placed in the capsular bag.

More than 93,000 units of the ReSTOR Toric IOL have been distributed in countries outside of the United States since June 2010. The ReSTOR Toric IOL is commercially available in the European Union, Japan, Australia, Canada, multiple countries within Central and South America, the Middle East, and the Far East. This product has not been withdrawn from any country for any reason.

A PMA Supplement for the ReSTOR Toric lens was submitted to the FDA in August of 2013. The PMA Supplement application included the data from Clinical Study C-09-036 which was initiated in September 2011. All aspects of the clinical study protocol were reviewed by FDA during the IDE review process; however, areas where FDA provided specific feedback were the control selection, randomization, safety endpoints, and PRO dossier design and development. Feedback received from FDA was reflected in the final clinical study protocol.

3 CLINICAL STUDY C-09-036

3.1 SUMMARY OF FINDINGS

Primary Effectiveness Endpoints

- The mean uncorrected distance visual acuity with the ReSTOR Toric IOL was 0.126 logMAR in the first eye, which was similar to that observed with the Control IOL (0.125 logMAR). The difference between groups was 0.001 logMAR with an upper CI of 0.030 meeting the clinical performance target of 0.1 logMAR. Findings with the second eye were similar.
- The mean uncorrected near visual acuity with the ReSTOR Toric IOL was 0.193 logMAR. The upper CI for the difference between the ReSTOR Toric IOL and the Control IOL was -0.017, meeting the performance target (≤ 0.1 logMAR). Findings for the second eye were similar; the mean uncorrected near visual acuity with the ReSTOR Toric IOL was 0.181 logMAR and the upper CI for the difference between the ReSTOR Toric IOL and Control IOL was -0.026.

Supportive Effectiveness Endpoints (descriptive statistics)

- Mean binocular uncorrected distance visual acuity was consistent between treatment groups with 0.03 logMAR observed for the ReSTOR Toric IOL versus 0.02 logMAR for the Control IOL.
- Mean binocular uncorrected near visual acuity was consistent between the ReSTOR Toric IOL and the Control IOL: 0.10 logMAR for the ReSTOR Toric IOL (at 40 cm) versus 0.14 logMAR for the Control IOL (at 33 cm).
- Mean binocular uncorrected visual acuity results demonstrated clinically relevant differences favoring the ReSTOR Toric IOL at 50 cm (0.13 logMAR for the ReSTOR Toric and 0.28 logMAR for the Control), 60 cm (0.17 logMAR for the ReSTOR Toric and 0.32 for the Control), and 70 cm (0.21 logMAR for the ReSTOR Toric and 0.32 for the Control).
- Best Corrected Binocular Defocus for the ReSTOR Toric IOL was consistent with functional vision (20/32 or better) over near, intermediate and distance (from 28 cm and beyond).
- In the ReSTOR Toric IOL group, 94.1% of subjects were within 1.0 D, and 74.5% within 0.5 D of their target cylinder for the first eye, and 97.6% of subjects were within 1.0 D, and 79.5% within 0.5 D of their target cylinder for the second eye.
- Increased spectacle independence post-operatively, as measured using Item 1 of the SILVER questionnaire, was 75.7% with the ReSTOR Toric IOL and 69.4% with the Control IOL.
- No difference in contrast sensitivity between the ReSTOR Toric IOL and Control IOL was observed under photopic and mesopic lighting conditions with and without a glare source.

Primary Safety Endpoints (descriptive statistics)

- The SSI rate due to optical properties was similar between groups. In the ReSTOR Toric IOL group, the overall rate of *actual* and *potential* SSIs due to optical properties of the IOL was 1.04% and 0.52% in the first and second eyes, respectively, based on the predefined Safety Data Set. In the Control IOL group, 2.13% and 2.13% had *actual* and *potential* SSIs due to the optical properties of the IOL in the first and second eye, respectively, also based on the predefined Safety Data Set.
- Rates of severe visual disturbances/distortions were similar between the ReSTOR Toric IOL (11.0%) and Control IOL (14.3%). The highest rate of severe visual disturbances/distortions at 12 months was for the category of halos, with a rate of 7.5% for the ReSTOR Toric IOL and 11.0% for the Control IOL.

3.2 STUDY DESIGN

Clinical Study C-09-036 was a prospective, nonrandomized, unmasked, parallel-group, multicenter study that enrolled adult subjects (21 years of age or older at the time of surgery) in need of cataract extraction in both eyes in which calculated lens power and corneal astigmatism were within the target range. The purpose of the study was to show that the addition of the toric surface would provide safety and efficacy results for patients with pre-existing astigmatism ≥ 0.75 D that are similar to those results expected with a control multifocal lens implanted in patients with minimal to no astigmatism (< 0.75 D). Corneal incisions to reduce corneal astigmatism were not permitted per the protocol during the study.

Subjects with ≥0.75 D of preoperative corneal astigmatism in both eyes and 0.75D – 2.82 D of predicted cross cylinder in both eyes received the ReSTOR Toric IOL, which included Models SND1T3/SND1T4/ SND1T5/SND1T6. Subjects with <0.75 D of preoperative corneal astigmatism in both eyes received the ReSTOR +4.0 D Multifocal IOL Model SA60D3 (Control IOL).

3.2.1 Control Selection

The purpose of Clinical Study C-09-036 was to demonstrate that the addition of a toric component to the ReSTOR Multifocal IOL could produce the same visual outcomes and safety profile in astigmatic patients as a multifocal control IOL could produce in non-astigmatic patients. The ReSTOR Multifocal IOL with +4.0 D of add power was selected as the control because it is the parent IOL for the ReSTOR Multifocal IOL family, which was originally approved under P040020. Key differences between the ReSTOR Toric IOL and the Control IOL are summarized in Table 7. These differences were taken into account during design of the study and, where applicable, during discussions of the outcomes of Clinical Study C-09-036.

Table 7. Key Device Differences between the ReSTOR Toric IOL and the Control IOL

ReSTOR Toric IOL	Control IOL
UV-absorbing acrylate/methacrylate copolymer with additional 0.4% covalently bondable yellow polymerizable dye	UV-absorbing acrylate/methacrylate copolymer
Posterior toric optical component to correct pre-existing corneal astigmatism	For non-astigmatic patients, no toric component
Incorporates an aspheric anterior surface to compensate for the spherical aberration of the human eye	Non-aspheric, does not compensate for corneal spherical aberration
Add Power at IOL plane is +3.0 D	Add Power at IOL plane is +4.0 D

3.2.2 Randomization and Masking

Clinical Study C-09-036 was neither randomized nor were the assessments masked. While it is acknowledged that both of these elements are hallmarks of sound clinical trial methodology, there are justifications for these choices that were carefully deliberated during study planning.

Randomization

The primary factor contributing to the decision not to implement a randomized study was the control IOL. The AcrySof ReSTOR IOL Model SA60D3 is not designed to correct for pre-existing corneal astigmatism. As indicated in Section 3.2.1 above, this was the selected Control IOL in the study because it is the parent lens and was the only multifocal lens available from Alcon without spherical aberration correction. The ability to assess the impact of asphericity on visual outcomes, if any, was considered important in the design of the ReSTOR Toric IOL confirmatory trial.

Given the refractive states intended to be treated by the ReSTOR Toric IOL and Control IOL, the subject population therefore necessarily consisted of persons with and without pre-existing corneal astigmatism with bilateral cataracts. It was therefore not possible to randomize subjects between these two treatment groups since it would have meant potentially undertreating some subjects (if there was ≥ 0.75 D of pre-existing corneal astigmatism and the subject was randomized to control), or treating with an IOL outside the indication for the subject's refractive state (if there was < 0.75 D of pre-existing corneal astigmatism and the subject was randomized to ReSTOR Toric). Consequently, eligible subjects received the IOL most suitable to effectively treat their refractive state.

The lack of randomization was acknowledged implicitly in the choice of primary analysis, to estimate outcomes rather than to implement more formal hypothesis testing for which a principal assumption is the comparison of randomized groups.

Masking

The consideration whether or not to implement masking in Clinical Study C-09-036, as with randomization, was related to the investigational products selected. The ReSTOR Toric IOL has physical attributes (toric markings to identify the IOL axis and correctly position the lens, and its yellow chromophore) that would have immediately unmasked it to the surgeon or investigator performing the ocular examination. As a surgically implanted device, it was not allowable to alter the appearance of either the ReSTOR Toric IOL or Control IOL in an attempt to conceal the identify of either product.

Even in such circumstances, however, it is not atypical to encounter situations where a technician who is responsible for collecting endpoint data remains masked to treatment received. For Clinical Study C-09-036, this, too, proved problematic for some of the study's assessments. Due to the difference in near focal point between the ReSTOR Toric IOL (40 cm) and Control (33 cm) IOL, best-corrected near visual acuity at fixed distance required IOL-specific testing distances. In addition, the lens axis orientation images captured with the PALO system were only to be done for ReSTOR Toric IOL since the Control IOL does not have toric markings. While it cannot be argued that it was not impossible to implement some measure of masking to assess some of the endpoints, the operational and logistical complexities of such an approach, as well as the clinical staffing needed to implement the approach, were believed to outweigh its added-value and the likelihood of truly maintaining masking for most subjects at investigative sites.

In summary, and notwithstanding any of the above in respect to randomization or masking, concerted efforts were taken to minimize the potential for bias in Clinical Study C-09-036. These included the application of customary principles in multicenter studies such as common inclusion/exclusion criteria across sites, standardized test procedures, and common investigator training.

3.2.3 Study Visits and Assessments

At the beginning of the study, subjects were implanted with either the ReSTOR Toric IOL or the Control IOL in their first eye. Per the protocol, the eye with the greater amount of astigmatism was to be implanted first. When possible, the second eye implant was intended to occur within 30 days after the first eye implant, but not prior to 7 days after the first eye implant, to allow sufficient time to diagnose and treat early postoperative complications such as endophthalmitis. Visits and eye examinations were conducted as listed in Table 8. Visual acuity testing was performed using ETDRS (logMAR) visual acuity charts. Distance vision was tested at 4 meters, and intermediate vision was tested at 50, 60, and 70 cm, measured from the subject's spectacle plane to the front surface of the near VA card. Near vision at fixed distance was tested at the designed near distance for each lens: 40 cm for the ReSTOR Toric IOL and 33 cm for the Control IOL. Methods to help control letter memorization include alternating reading direction (left to right; right to left) and use of different visual acuity charts (2 for near and 2 for distance) with letter sequence variations.

Table 8. Eye Examination and Follow-up Schedule

Time From Implantation	Visit Number
Preoperative	Visit 0 (monocular and binocular)
Operative	Visit 00
1 - 2 days	Visit 1
7 - 14 days	Visit 2
30 - 60 days	Visit 3 (monocular-1st eye)
120 - 180 days (after 2nd eye implant)	Visit 4 (monocular and binocular)
330 - 420 days (after 2nd eye implant)	Visit 5 (monocular and binocular)

Increased spectacle independence was demonstrated in this astigmatic patient population as it was in the non-astigmatic patient population in the prior ReSTOR Multifocal IOL submissions (PMA P040020 and P040020/S012). Increased spectacle independence for the astigmatic population was evaluated using Item 1 from the 11-item SILVER patient-reported outcomes (PRO) questionnaire. SILVER Item 1, "How often do you wear eyeglasses or contact lenses overall" supports the product's indications for use by assessing increased overall spectacle independence in patients with an implanted IOL. SILVER was administered at Visits 0 (preoperative), 4 (6 months), and 5 (12 months) and at unscheduled visits. Development and psychometric evaluation of SILVER was aligned with the 2009 FDA "Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims". The development and psychometric evaluation of SILVER is discussed in more detail in Section 3.2.4.2.

All postoperative ocular observations were derived from slit lamp, indirect, and direct ophthalmoscopy (dilated fundus examination). Subjects underwent a dilated fundus exam at Visit 0, Visit 3, Visit 4, and Visit 5. Investigators also identified all AEs including all SSIs. The definition for SSIs due to optical properties was developed based upon discussions and feedback received from the FDA:

- IOL misalignment or rotation
- IOL tilt and decentration
- Visual disturbances and distortions
- Unanticipated refractive outcomes

The types of secondary surgical interventions the IOL included IOL repositioning and IOL replacement.

Photographic Assessment of Lens Orientation (PALO) is a proprietary software tool used to measure toric IOL orientation for the clinical study. The PALO software allowed the operator to select the toric lens markers and anatomical landmarks on the eye and use their coordinate locations to yield a

quantitative measure of the axis of orientation for the implanted IOL. PALO is 21 CRF Part 11 compliant and established in a clinical setting for reliability and repeatability.

Visual disturbances/distortions were assessed in terms of frequency and severity using the 21-item APPLES PRO questionnaire. APPLES was administered to each patient at the Pre-operative Visit, Visit 4, Visit 5, at any unscheduled visit after 3 months, and prior to any secondary surgical intervention. Development and psychometric evaluation of APPLES was aligned with the 2009 FDA "Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims". The development and psychometric evaluation of APPLES is discussed in more detail in Section 3.2.4.3.

3.2.4 Study Endpoints

The co-primary effectiveness endpoints were the mean monocular UCDVA and mean monocular UCNVA at fixed distance for the first operative eye. Per the protocol, the differences between the ReSTOR Toric IOL and the concurrent Control IOL for UCDVA and UCNVA had to be less than 0.1 logMAR at 12 months post-implant to establish the effectiveness of the ReSTOR Toric IOL. The non-inferiority margin of 0.1 logMAR, corresponding to 1 line on an ETDRS visual acuity chart, was chosen as changes of less than 0.1 logMAR have been studied and are not considered to be clinically relevant (Vanden Bosch 1997, Arditi and Cagenello 1993, Bailey 1991, Beck 2007, Forooghian 2009, Sakatani 2004, Mohamed 2011).

Additional effectiveness endpoints included the following:

- Near, Intermediate, and Distance visual acuity:
    - Monocular (Best Corrected) and Binocular (Uncorrected and Best Corrected) Distance Visual Acuity
    - Monocular (Distance Corrected for optical infinity and Best Corrected) and Binocular (Uncorrected, Distance Corrected for optical infinity and Best Corrected) Near Visual Acuity at Fixed Distance and Monocular and Binocular Near Visual Acuity at Best Distance: Uncorrected and Distance Corrected for optical infinity
    - Monocular and Binocular Mesopic Near Visual Acuity at Best Distance: Distance Corrected for optical infinity
    - Binocular Intermediate Visual Acuity (50 cm, 60 cm, and 70 cm): Uncorrected and Distance Corrected for optical infinity
- Reduction of cylinder (ReSTOR Toric IOL only)
- Increased Spectacle Independence - as determined by Item 1 from the SILVER Questionnaire (*How often do you wear eyeglasses or contact lenses overall?")*
- IOL rotation and misalignment - as determined by Photographic Assessment of Lens Orientation (PALO) (ReSTOR Toric IOL only)
- Contrast Sensitivity (Photopic and Mesopic with and without glare)

- Binocular Defocus (+2.0 D to -5.0 D in 0.5 D increments)

The primary safety objective was to estimate the rate of actual and potential SSIs related to optical properties of the IOL for first and second operative eyes separately at 12 months (Visit 5) post-implant. The secondary safety objective was to estimate the rate of severe visual disturbances/distortions as reported by subject responses to the APPLES questionnaire at 12 months (Visit 5) post-implant.

The supportive safety endpoints included the following:

- AEs including UADEs and Device Deficiencies
- Surgical Problems
- Subjective PCO Assessment and Capsulotomy

3.2.4.1 Patient Reported Outcomes: SILVER and APPLES

Clinical Study C-09-036 utilized two different Patient Reported Outcome (PRO) questionnaires: the *Spectacle Independence Lens Vision Evaluation and Repurchase* (SILVER) and *Assessment of Photic Phenomena and Lens Effects* (APPLES). The SILVER questionnaire supports effectiveness parameters by assessing increased spectacle independence. The APPLES questionnaire supports safety parameters by assessing visual disturbances. Both questionnaires were developed to reflect the study population of patients in need of cataract extraction in both eyes and implanted with monofocal, multifocal, or toric IOLs. The recall period for the patient responses in both SILVER and APPLES is one week. Investigators were trained with a standard operating procedure for data collection for the SILVER and APPLES questionnaires at the clinical study's investigator meeting. The SILVER and APPLES questionnaires were completed by the patients using pen and paper.

SILVER and APPLES were developed in alignment with the 2009 FDA Guidance, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"

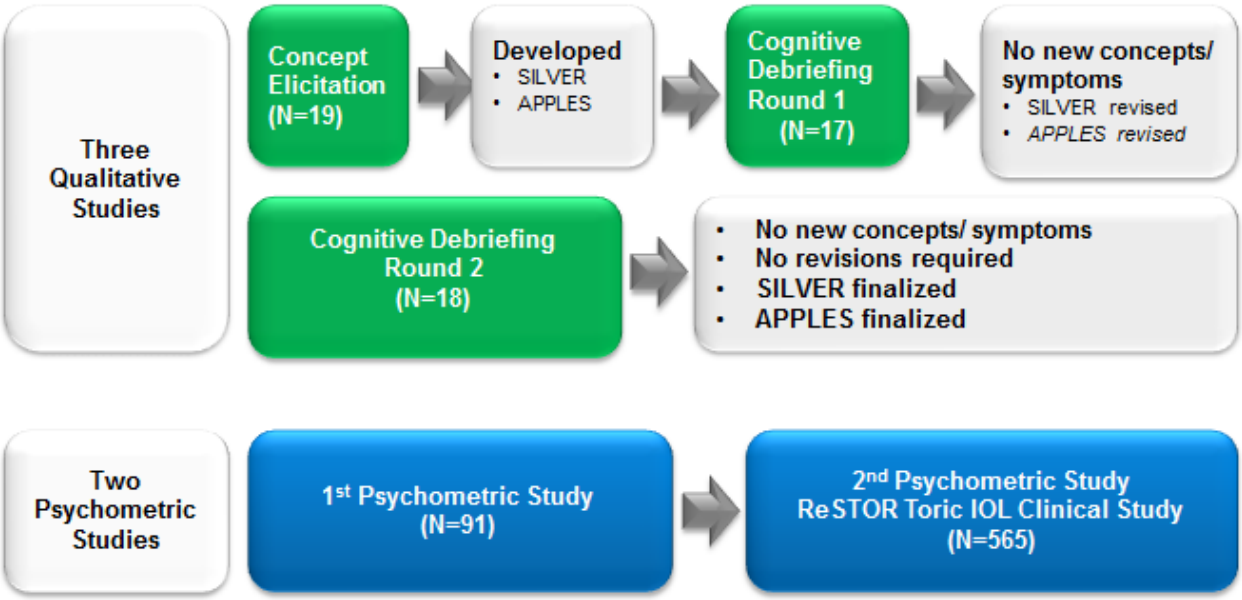
These questionnaires were developed for Clinical Study C-09-036 to assess increased spectacle independence and visual disturbances. The Cataract TyPE Specification (Cataract TyPE) (Javitt 1997) and the Quality of Vision (QoV) (McLinden 2010) were initially considered for this study as the Cataract TyPE had been previously used by Alcon to support efficacy, and the QoV captured many of the safety concerns associated with intraocular lenses. They both were determined not to be adequate to assess these safety and effectiveness outcomes in patients following cataract removal and implantation with presbyopia-correcting multifocal IOLs or astigmatism-correcting toric monofocal IOLs.

The SILVER and APPLES PROs were developed based on three qualitative studies involving concept elicitation to identify relevant concepts, and cognitive interviewing to evaluate patient understanding of the items, response scales, and instructions (Figure 11). The psychometric evaluation of SILVER and APPLES was conducted in a single stand-alone observational study with 91 subjects who had a clinical diagnosis of cataracts and received newly implanted IOLs. These subjects were implanted with bilateral

multifocal and toric IOLs including bilaterally implanted monofocal IOLs with < 1.0 D of astigmatism; bilaterally implanted multifocal IOLs with < 1.0 D of astigmatism; and bilaterally implanted Alcon monofocal Toric IOLs with 1.0 D - 2.5 D of preoperative astigmatism.

The study population for the qualitative and psychometric studies for SILVER and APPLES reflected those in Clinical Study C-09-036; additionally, the study populations were consistent with those undergoing cataract surgery (Lundstrom 2013) and in previous Alcon cataract studies. A second confirmatory psychometric analysis was conducted to evaluate the psychometric characteristics of the two questionnaires based on data collected in the Clinical Study C-09-036, that is, 565 subjects who received newly implanted ReSTOR Toric IOLs or the Control IOL. Findings from the two psychometric analyses confirmed and further supported the reliability of SILVER and APPLES among clinically diagnosed cataract patients implanted with bilateral multifocal and multifocal toric IOLs. Although different factor structures were explored for the APPLES, focus was on the single items only for purposes of monitoring symptoms for safety.

Figure 11. Development of the APPLES and SILVER PRO Questionnaires



3.2.4.2 Description of the SILVER PRO

SILVER is an 11-item PRO questionnaire developed to evaluate frequency of spectacle use, quality of vision, satisfaction with vision, and subject willingness to have the same lens model implanted again. This questionnaire was developed in alignment with the 2009 FDA PRO Guidance. SILVER Item 1: "*How often do you wear eyeglasses or contact lenses overall?*" was identified to support the product indication

of increased spectacle independence. Use of "overall" was selected to assess increased spectacle independence with the ReSTOR Toric IOL for several reasons. First, the PRO utilized during previous studies of the ReSTOR Multifocal lenses (PMA P040020 and P040020/S012) used similar language. Secondly, "overall" represents the most conservative criteria in that it represents a range of distances and was identified as the most appropriate and conservative to determine increased spectacle independence.

Initially, the Cataract TyPE Specification Questionnaire (Javitt 1997), which was previously utilized by Alcon to support increased spectacle independence in IOL clinical studies, was identified to be used as it was designed to measure outcomes in cataract patients. However, as the instrument was not developed or validated in cataract patients implanted with bilateral multifocal, toric, and monofocal intraocular lenses, and because the original development work was not available to support modifications necessary for Clinical Study C-09-036, a new questionnaire, the SILVER, was determined to be appropriate for use in this clinical study setting.

Psychometric evaluation for SILVER was conducted as a stand-alone study utilizing the SILVER, APPLES and other ancillary measures including the Refractive Status and Vision Profile (RSVP) (Schein 2001; Schein 2000; Vitale 2000). The RSVP is a questionnaire designed to measure functioning, symptoms, health perceptions, and expectations in individuals with refractive error; and it is referenced in the 2010 ANSI Toric Lens Standards with regards to distortion. Because the RSVP was developed and validated in patients with refractive error only and not in cataract patients implanted with bilateral multifocal, toric, and monofocal intraocular lenses, the RSVP was not appropriate for use to measure increased spectacle independence in Clinical Study C-09-036.

For the initial psychometric analysis of the SILVER, Item 1 demonstrated test-retest reliability. Results indicate that there were no significant differences in scores between the two assessments (i.e., Days 1 and 7), with ICCs of 0.87, which indicates a strong concordance between the two time points. Correlations were low between SILVER Item 1 and visual acuity, however, SILVER demonstrated known groups validity, whereby scores for SILVER Item 1 were examined by patient global ratings of overall visual symptom severity. Scores for SILVER Item 1 were significantly different by patient rated global severity (very poor/poor/fair) vs (good/very good) with $p < 0.005$.

The confirmatory psychometric analysis for SILVER utilized the clinical trial data and confirmed that the results from this analysis for SILVER were comparable to the results of the initial psychometric study.

3.2.4.3 Description of the APPLES PRO

APPLES is a 21 item PRO questionnaire used to support the clinical study's secondary safety endpoint of severe visual disturbances/distortions by assessing visual phenomena in terms of frequency and severity. Development and psychometric evaluation for APPLES was in alignment with the 2009 FDA

PRO Guidance. This questionnaire addresses the frequency and the severity of 10 symptoms: glare, halos, starbursts, hazy vision, blurred vision, distortion where straight lines looked tilted, distortion where flat surfaces look curved, double vision, color distortion, and queasiness due to visual distortions. Reference pictures representing how "normal vision" and "symptom" might appear were included in APPLES for eight of the ten symptoms. Based on feedback received from FDA during the IDE review process, Alcon incorporated an item on "other symptoms" to measure symptoms not captured by APPLES. Frequency and severity response options are based upon a 4-point Likert scale. The APPLES items instructed the respondent to rate symptoms associated with their vision in the last week without glasses or contact lenses. Scoring for APPLES is by individual items and no total score is calculated. These symptoms were developed based upon direct patient input.

The Quality of Vision (QoV) PRO questionnaire was considered for assessing visual disturbances because it measures some of the relevant symptoms for Clinical Study C-09-036. This questionnaire was developed and validated by McAlinden et al. (2010) in patients from the United Kingdom with refractive correction, eye surgery, and eye disease resulting in quality of vision problems. Results from the initial concept elicitation qualitative interviews of the QoV indicated that a number of revisions would be necessary to ensure that the items and response options were clear and easy to understand. These findings and input received from FDA during the IDE review process regarding distortions and provision for spontaneous patient reporting of severe visual symptoms determined that a new questionnaire, the APPLES, and not the QoV, was appropriate for the intended study population. The APPLES was developed based upon concept elicitation and cognitive interviewing in patients that were similar to those recruited into the clinical study (Figure 11).

Psychometric evaluation of the APPLES was conducted in a stand-alone psychometric study utilizing the APPLES and other ancillary measures including the RSVP questionnaire referenced in Section 3.2.4.2 above. Because the RSVP was developed and validated in patients with refractive error only and not in cataract patients implanted with bilateral multifocal, toric, and monofocal intraocular lenses, the RSVP was never considered a candidate for use in measuring the visual disturbances in Clinical Study C-09-036.

For this initial psychometric analysis: factor analysis, internal consistency reliability, test-retest reliability, and known groups validity were evaluated. Regarding each of the symptoms, patients used the full range of response options for all items, except for those related to distortion. A floor effect (i.e., never experienced during past week) was noted for at least 95% of the sample for all distortion items (distortion where straight lines look tilted, distortion where flat surfaces look curved, color distortion, and feeling sick to the stomach due to visual distortions), suggesting that these were symptoms not commonly experienced by this patient population. These items were included in APPLES based upon discussions between Alcon and the FDA as toric IOLs may be associated with spatial distortion related to axial misalignment as specified in the 2010 ANSI IOL Toric Standards. These items were tested in the

cognitive interview phase of the instrument development and were included based upon potential of patient experience of these symptoms. APPLES demonstrated low to moderate correlations with the RSVP domains of driving, symptoms, and glare. Correlations between individual symptoms and patient-rated global visual symptom severity were low to moderate for all items except the distortion items.

Overall, none of the individual symptoms (i.e., glare, halos, etc.) were highly correlated to each other ($r \geq 0.80$) suggesting that the items measured different concepts. This low correlation was anticipated as the items measured different side effects or symptoms. Exploratory factor analyses for both frequency and severity of the symptom items indicated that the scales were not unidimensional. Although different factor structures were explored for the APPLES, focus was on the single items only for purposes of monitoring symptoms for safety. As each item measured a unique concept, each item must be scored separately for frequency and severity.

Based on the clinical trial data, APPLES scores were correlated with clinical outcomes. Results demonstrated that several APPLES items were positively correlated with binocular uncorrected distance and near visual acuity scores, such that individuals with poorer visual acuity reported more frequent and/or severe symptoms.

3.2.5 Inclusion/Exclusion Criteria

Inclusion/exclusion criteria applied to both eyes at the preoperative visit. If the subject's first eye was excluded during surgery, the subject's second eye was not eligible. If the subject's second eye was excluded during surgery, only the first eye was to be followed in the study.

The inclusion criteria were as follows:

1) Twenty-one years of age or older at the time of surgery and diagnosed with bilateral cataracts
2) Able to comprehend and sign a statement of informed consent
3) Calculated lens power and corneal astigmatism within the available range
4) Willing and able to complete all required postoperative visits
5) Planned cataract removal by phacoemulsification
6) Potential postoperative visual acuity of 0.2 logMAR or better in both eyes
7) Preoperative corneal astigmatism of ≤ 0.74 D as described in Table 9, measured by the IOLMaster optical biometry instrument (Carl Zeiss Meditec, Inc., Dublin, California) in both operative eyes for the AcrySof Control IOL Model SA60D3

   -Or-

   Preoperative corneal astigmatism of ≥ 0.75 D, measured by the IOLMaster optical biometry instrument (Carl Zeiss Meditec, Inc., Dublin, California) in both operative eyes and 0.75 D - 2.82 D of predicted crossed cylinder in both operative eyes calculated by the study specific web-based ReSTOR Toric Clinical Calculator for the Control IOL Models SND1T3-SND1T6 and as

described in Table 9; any subjects that did not meet corneal astigmatism ranges for first and second eye in Table 9 were excluded.

8) Clear intraocular media other than cataract in study eyes
9) Preoperative BCDVA worse than 0.2 logMAR in each eye
10) Pupil size greater than or equal to 6 mm after dilation
11) The subject must have been able to undergo second eye surgery within 30 days of the first eye surgery

Table 9. Corneal Astigmatism Range/Lens Model: First Eyes and Second Eyes

First Eye Corneal Astigmatism Correction Range	First Eye Lens Model	Second Eye Corneal Astigmatism Correction Range	Second Eye Lens Model Option
Control Lens			
0.00 D-0.74 D	SA60D3	0.00 D-0.74 D	SA60D3 only
Investigational Lenses			
0.75 D-1.28 D	SND1T3	0.75 D-1.28 D	SND1T3 only
1.29 D-1.80 D	SND1T4	0.75 D-1.80 D	SND1T3 or SND1T4
1.81 D-2.32 D	SND1T5	1.29 D-2.32 D	SND1T4 or SND1T5
2.33 D-2.82 D	SND1T6	1.81 D-2.82 D	SND1T5 or SND1T6

The exclusion criteria were as follows:

1) Significant irregular corneal aberration as demonstrated by corneal topography
2) Keratopathy/Kerectasia - any corneal abnormality, other than regular corneal astigmatism, including, but not limited to the following: keratoconus, keratoglobus, keratolysis, keratomalacia, keratomycosis, and corneal plana
3) Any inflammation or edema (swelling) of the cornea, including but not limited to the following: keratitis, keratoconjunctivitis, and keratouveitis
4) Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted (by subjective assessment of the retina) to cause future acuity losses to a level worse than 0.2 logMAR
5) Subjects who may have reasonably been expected to require a secondary surgical intervention at any time during the study (other than YAG capsulotomy)
6) Previous corneal refractive surgery
7) Amblyopia
8) Clinically severe corneal dystrophy (e.g., epithelial, stromal, or endothelial dystrophy)
9) Diabetic retinopathy

10) Extremely shallow anterior chamber, not due to swollen cataract
11) Microphthalmos
12) Previous retinal detachment
13) Previous corneal transplant
14) Recurrent severe anterior or posterior segment inflammation of unknown etiology
15) Rubella or traumatic cataract
16) Iris neovascularization
17) Glaucoma (uncontrolled or controlled with medication)
18) Aniridia
19) Optic nerve atrophy
20) Pregnancy
21) Any subject participating in another investigational drug or device study that may have confounded the results of this investigation
22) Other planned ocular surgery procedures, including, but not limited to LASIK, astigmatic keratotomy and limbal relaxing incisions, for the duration of the study

Exclusion Criteria during Surgery

23) Any incision site other than temporal (±15° from the horizontal meridian)
24) Other ocular surgery procedures, including, but not limited to LASIK, astigmatic keratotomy and limbal relaxing incisions, for the duration of the study
25) Mechanical or surgical manipulation required to enlarge the pupil; pupil size was required to be at least 4.5 mm or larger just prior to IOL implantation
26) Significant vitreous loss
27) Significant anterior chamber hyphema
28) Uncontrollable intraocular pressure
29) Zonular or capsular rupture
30) Bag-sulcus, sulcus-sulcus or unknown placement of the haptics

3.2.6 Statistical Methodology

3.2.6.1 Sample Size Justification

The primary driver of sample size for this study was the precision of the confidence interval on the rate of actual or potential secondary surgical interventions related to optical properties of the IOL. The study was designed such that the event rate in the ReSTOR Toric IOL group could be estimated to as low as approximately 1% with 95% confidence. With 300 first-operative eyes in the ReSTOR Toric IOL group, if zero (0) events were observed, the 95% 1-sided exact Binomial upper confidence limit would be less

than 0.01, meaning we could be 95% confident that the true adverse event rate was less than 0.01 if zero (0) events were observed.

As discussed with the FDA prior to initiation of the study, there was no prespecified definition for success in interpreting the rate of SSIs due to optical properties observed in the study. Clinical judgment would consider the rate of SSIs due to optical properties within the context of the benefit provided with the ReSTOR Toric IOL to assess the overall benefit-risk of the product. A minimum of 340 subjects were to be bilaterally implanted with the ReSTOR Toric IOL in order to ensure at least 300 eligible subjects completed the study. This assumed a drop-out rate of 10% (34 subjects). In the control group, a minimum of 170 subjects were to be bilaterally implanted with the Control IOL. Because four models of the ReSTOR Toric were included in Clinical Study C-09-036, target sample sizes were defined for each model as summarized in Table 10.

Table 10. Sample Size per IOL Model Included in Clinical Study C-09-036

Lens Model (1st operative eye)	Recommended Corneal Astigmatism Correction Range	Number of Subjects	
		Minimum per Model	Minimum per Group
Control Lens			
SA60D3	0.00 D-0.74 D	170	170
Investigational Lenses			
SND1T3	0.75 D-1.28 D	70	240 (≤ 2.0 D of corneal astigmatism at the corneal plane)
SND1T4	1.29 D-1.80 D	70	
SND1T5	1.81 D-2.32 D	20	100 (> 2.0 D of corneal astigmatism at the corneal plane)
SND1T6	2.33 D-2.82 D	20	

3.2.6.2 Definition of Analysis Datasets

Analysis datasets were predefined as follows:

- Safety dataset: All eyes with attempted IOL implantation in at least one eye where the lens touched the eye
- All implanted dataset: All eyes with successful IOL implantation in at least one eye - primary data set of analysis for effectiveness endpoints
- Best case dataset: All eyes successfully implanted that have at least one postoperative visit and have no preoperative pathology or macular degeneration at any time - primary data set of analysis for binocular defocus and contrast sensitivity

3.2.6.3 Summary of Statistical Analysis

The primary effectiveness analysis was conducted for monocular UCDVA and monocular UCNVA at fixed distance in the *All Implanted* dataset for the first operative eye at 12 months (Visit 5). For each parameter, the difference in means (ReSTOR Toric IOL minus Control IOL) and the corresponding one-sided upper 95% confidence limit for the difference were estimated using ANCOVA, and the upper limit was compared to a clinical performance target of 0.1 logMAR. Age, site, and spherical equivalent lens power (in diopters) were included as covariates in the ANCOVA model. Per the analysis plan, the interaction between site and treatment was to be included in the primary effectiveness models if the interaction was significant at the 0.15 level. As the interaction term was significant at the 0.15 level for both models, it was included as a random effect in the analysis of both primary endpoints (UCDVA and UCNVA on first eyes). Treatment differences were calculated using least square mean differences. Results were considered successful if the upper limit for each co-primary parameter was less than the clinical performance target. Since the clinical performance target had to be met for both UCDVA and UCNVA, no multiplicity adjustment was required. Analysis of the second eye was independent of the first, with a separate check of treatment site interaction. There was no statistical evidence of interaction for analysis of the second eye, so site was not included in the model.

The primary effectiveness analysis included ReSTOR Toric IOL subjects from all lens models (SND1T3/ SND1T4/SND1T5/SND1T6) combined. Subgroup analyses were conducted by lens power subgroup (i.e., combined SND1T3-SND1T4 groups and combined SND1T5-SND1T6 groups). Additional efficacy and safety endpoints were evaluated using descriptive statistical methods with no formal hypothesis testing. No interim analyses were performed.

For the primary analysis of UCDVA and UCNVA, subjects with missing data at Visit 5 were excluded from analysis. No imputation was planned or performed for subjects who had missing VA data at Visit 5. Sensitivity analyses were conducted to evaluate the impact of missing data, however. These included: 1) imputing the missing data point(s) with the median value of all postoperative visits for the subject, and 2) imputing the missing data point(s) for a test group subject with the worst postoperative value from all test group subjects, and the missing data point(s) for a control group subject with the best postoperative value from all control group subjects. These two sensitivity analyses impute missing data differently. Method 1 imputes missing data with the median of observed data from only that subject and method 2 imputes missing data with the extreme of data observed from all subjects. Because of this difference, method 2 can be used to impute missing data for subjects who had no available data after implantation, but method 1 cannot. This will result in different denominators in the various sensitivity analyses. Three subjects cannot contribute to the sensitivity analysis of UCNVA in the first eye using method 1 due to lack of any available data after implantation, and 1 subject cannot contribute to the sensitivity analysis of UCNVA in the second eye using method 1 for the same reason. However, all 4 of these eyes are included in the sensitivity analyses of UCDVA using method 1 due to available data on this endpoint, and

all are included in all sensitivity analyses using method 2 due to the different imputation method. The effectiveness endpoints were also examined by model. The SND1T3/SND1T4 and SND1T5/SND1T6 models were combined.

For the primary safety analysis, all data from eyes where the lens touched the eye were included in the analysis even if the subject discontinued the study. If the actual or potential SSI was recorded before the subject discontinued, then the event was included in the analysis. Subjects without events who discontinued were imputed with an outcome of "no SSI" through the end of the study.

The SILVER and APPLES questionnaires were evaluated using descriptive analyses. SILVER describes increased spectacle independence. APPLES describes percent of subjects with severe symptoms.

3.3 DISPOSITION

Overall, 677 subjects were screened for entry into Clinical Study C-09-036 (Figure 12). Of the 677 subjects that were screened for entry and signed an informed consent, 574 met all inclusion and exclusion criteria. Of the 574 subjects implanted with either the investigational ReSTOR Toric IOL or Control IOL, 19 subjects discontinued without 12 month follow up data (Table 11). Available data for all 19 subjects was included in the primary analysis of safety as predefined in the statistical analysis plan. Subjects were counted as having an actual or potential SSI for the primary safety analysis if such an event was recorded at any time during which the subject was followed.

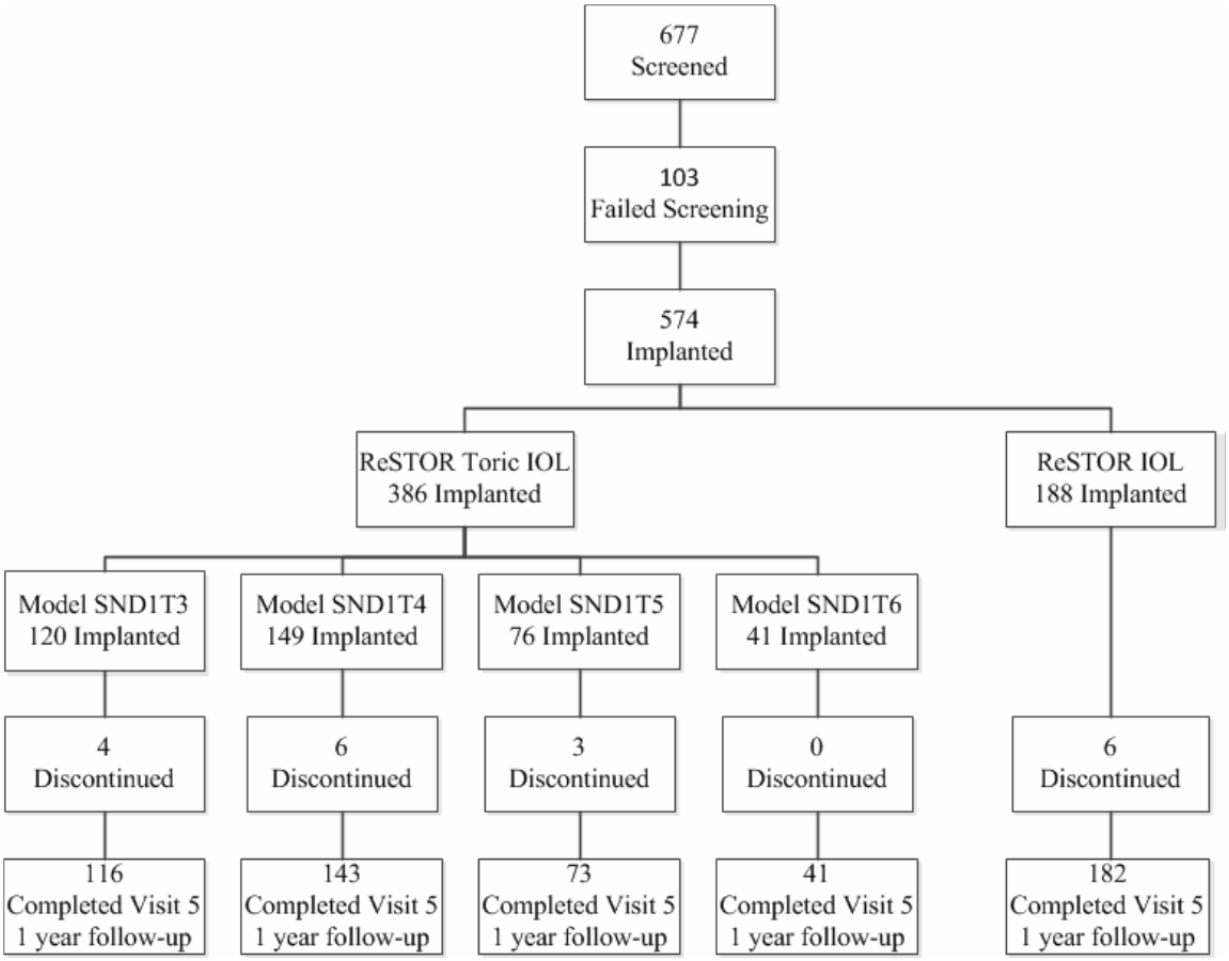
There was no significant difference in discontinuation rates between treatment groups. Of the 386 subjects implanted with the ReSTOR Toric IOL, 13 (3.4%) discontinued before the 1-year follow-up was completed, and of the 188 implanted with the Control IOL, 6 (3.2%) discontinued. In the ReSTOR Toric IOL group, 1 subject discontinued due to an AE, 4 were lost to follow-up, 4 no longer wished to participate, 1 moved or was unable to make future office visits, and 3 died. In the Control IOL group, 1 was lost to follow-up, 4 no longer wished to participate, and 1 died. All deaths were considered by investigators to be unrelated to the device.

Table 11. Patient Disposition in Study C 09-036

	ReSTOR Toric IOL (N = 386)		Control IOL (N = 188)	
	n	(%)	n	(%)
Completed	373	(96.6)	182	(96.8)
Discontinued	13	(3.4)	6	(3.2)
Adverse Event	1	(0.3)	0	(0.0)
Lost to Follow-up	4	(1.0)	1	(0.5)
Subject No Longer Wishes to Participate	4	(1.0)	4	(2.1)
Unable to Make Future Office Visits / Moved	1	(0.3)	0	(0.0)

Subject Died	3	(0.8)	1	(0.5)

Figure 12. Subject Disposition and Accountability at 1 year of Follow-up



3.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Age, gender, and race distribution of subjects are consistent with the target population for this lens (Table 12). Both groups had a larger percentage of female subjects and the majority of subjects were between the ages of 60 and 79. Baseline visual acuity results were similar by treatment group, with both the ReSTOR Toric IOL and Control IOL groups having 20/50 Snellen mean best corrected visual acuity in the first and second eye (ReSTOR Toric IOL group mean visual acuity; 0.38 logMAR in the first and 0.36 logMAR in the second eye and Control IOL group mean visual acuity; 0.39 logMAR in the first and 0.36 logMAR in the second eye).

Table 12. Demographic Characteristics

	ReSTOR Toric IOL (N = 386) n (%)		Control IOL (N = 188) n (%)	
Age categories (in years)				
21-29	2	(0.5)	0	(0.0)
30-39	3	(0.8)	0	(0.0)
40-49	10	(2.6)	3	(1.6)
50-59	57	(14.8)	24	(12.8)
60-69	155	(40.2)	73	(38.8)
70-79	135	(35.0)	76	(40.4)
≥80	24	(6.2)	12	(6.4)
Gender				
Male	146	(37.8)	52	(27.7)
Female	240	(62.2)	136	(72.3)
Race				
White	362	(93.8)	176	(93.6)
Black or African American	14	(3.6)	12	(6.4)
Asian	5	(1.3)	0	(0.0)
Other	5	(1.3)	0	(0.0)
Ethnicity				
Hispanic, Latino or Spanish	6	(1.6)	3	(1.6)
Not Hispanic, Latino or Spanish	380	(98.4)	185	(98.4)

3.5 EFFECTIVENESS FINDINGS

For subjects with preexisting corneal astigmatism ≥ 0.75 D, the ReSTOR Toric IOL was effective at providing vision from near, through intermediate to distance. Near and distance visual acuity results for

the ReSTOR Toric IOL were consistent with those observed with the Control IOL. The results were consistent across ReSTOR Toric IOL models.

3.5.1 Visual Acuity

Visual acuity testing was performed using 100% contrast ETDRS (logMAR) visual acuity charts. Visual acuity measurements at distance were performed using 4 m ETDRS charts. For near visual acuity testing, a 40 cm ETDRS chart was used; testing was performed at 40 cm for the ReSTOR Toric IOL and 33 cm for the Control IOL (results obtained were converted to reflect the change in apparent letter size that results from the change in distance from 40 cm to 33 cm). All intermediate vision tests were performed binocularly at either 50 cm, 60 cm, or 70 cm. The ETDRS visual acuity chart used for intermediate visual acuity was designed for a 40 cm test distance, therefore, the results obtained at all intermediate distances were converted to reflect the change in apparent letter size that results from the change in distance. Table 13 provides Snellen equivalencies by logMAR range.

Table 13. LogMAR and Snellen Equivalent

logMAR	Snellen
-0.25 to -0.16	20/12.5
-0.15 to -0.06	20/16
-0.05 to 0.04	20/20
0.05 to 0.14	20/25
0.15 to 0.24	20/30
0.25 to 0.34	20/40
0.35 to 0.44	20/50
0.45 to 0.54	20/63
0.55 to 0.64	20/80
≥ 0.65	worse than 20/80

3.5.1.1 Primary Outcomes: UCDVA and UCNVA

Comparison of visual acuity between ReSTOR Toric and the Control IOL met prespecified clinical performance criteria for both UCDVA and UCNVA (at fixed distance) in the first eye (Table 14 and Table 15). The difference between the ReSTOR Toric IOL and the Control IOL for UCDVA in the first eye was 0.001 logMAR with an upper CI of 0.030 meeting the clinical performance target 0.1 logMAR. Similar findings were observed for UCNVA at fixed distance in the first eye, where the upper CI was -0.017. Findings with the second eye were consistent with those of the first eye. Both treatment groups achieved 20/25 Snellen visual acuity at distance and 20/32 Snellen acuity at near in the first implanted eye.

Table 14. Comparison of Monocular Uncorrected Distance Visual Acuity at 12 Months (Visit 5) Using Least Squares Estimates (All Implanted Population)

		ReSTOR Toric IOL (N=386)	Control IOL (N=186)	Difference (95% UCL)
First Implanted Eye	N	373	180	
	Mean	0.126	0.125	0.001 (0.030)
	SE	0.013	0.015	
Second Implanted Eye	N	371	180	
	Mean	0.113	0.102	0.011 (0.038)
	SE	0.011	0.013	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on the repeated measure analysis of covariance
UCL = 95% Upper confidence limit; SE = Standard error
"(N=)" in column header is number in the treatment group. Subjects who discontinued before Visit 5 are excluded from this analysis. Numbers with data are indicated in the table body.

Table 15. Comparison of Monocular Uncorrected Near Visual Acuity at Fixed Distance at 12 Months (Visit 5) Using Least Squares Estimates (All Implanted Population)

		ReSTOR Toric IOL (N=386)	Control IOL (N=186)	Difference (95% UCL)
First Implanted Eye	N	373	180	
	Mean	0.193	0.236	-0.044 (-0.017)
	SE	0.015	0.017	
Second Implanted Eye	N	371	180	
	Mean	0.181	0.234	-0.052 (-0.026)
	SE	0.013	0.015	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on the repeated measure analysis of covariance
UCL = 95% Upper confidence limit; SE = Standard error
"(N=)" in column header is number in the treatment group. Subjects who discontinued before Visit 5 are excluded from this analysis. Number with data are indicated in the table body.

Analyses were also conducted to evaluate the ReSTOR Toric IOL Models SND1T3/ SND1T4 and Models SND1T5/ SND1T6. All 12 month (Visit 5) findings were consistent by model. Summary statistics by model and visit for UCDVA are provided in Table 16. Findings for UCNVA were similar but are not presented.

Table 16. Summary of UCDVA by Lens Model and Visit (All Implanted Population)

		First Implanted Eye		Second Implanted Eye	
		SND1T3/SND1T4	**SND1T5/SND1T6**	**SND1T3/SND1T4**	**SND1T5/SND1T6**
Visit 1	n	269	117	316	66
	Mean (SD)	0.23 (0.18)	0.26 (0.21)	0.20 (0.17)	0.18 (0.20)
	(Min, Max)	(-0.12, 0.90)	(-0.08, 1.00)	(-0.18, 0.86)	(-0.06, 0.92)
	95% CI	(0.20, 0.25)	(0.22, 0.30)	(0.18, 0.22)	(0.13, 0.23)
Visit 2	n	269	117	316	66
	Mean (SD)	0.14 (0.15)	0.16 (0.15)	0.12 (0.15)	0.13 (0.15)
	(Min, Max)	(-0.14, 0.80)	(-0.18, 0.68)	(-0.20, 0.70)	(-0.18, 0.56)
	95% CI	(0.12, 0.16)	(0.14, 0.19)	(0.11, 0.14)	(0.09, 0.16)
Visit 3	n	267	116	316	66
	Mean (SD)	0.11 (0.13)	0.15 (0.16)	0.11 (0.14)	0.12 (0.15)
	(Min, Max)	(-0.16, 0.52)	(-0.08, 0.90)	(-0.22, 0.72)	(-0.10, 0.80)
	95% CI	(0.10, 0.13)	(0.12, 0.18)	(0.09, 0.12)	(0.08, 0.16)
Visit 4	n	265	114	311	66
	Mean (SD)	0.12 (0.15)	0.15 (0.16)	0.11 (0.14)	0.12 (0.14)
	(Min, Max)	(-0.16, 0.80)	(-0.10, 0.72)	(-0.18, 0.76)	(-0.14, 0.60)
	95% CI	(0.10, 0.13)	(0.12, 0.18)	(0.09, 0.13)	(0.08, 0.16)
Visit 5	n	260	113	306	65
	Mean (SD)	0.12 (0.14)	0.15 (0.16)	0.11 (0.14)	0.13 (0.14)
	(Min, Max)	(-0.12, 0.62)	(-0.20, 0.74)	(-0.18, 0.76)	(-0.06, 0.66)
	95% CI	(0.10, 0.13)	(0.12, 0.18)	(0.09, 0.12)	(0.09, 0.16)

3.5.1.2 Supportive Near and Distance Visual Acuity Outcomes

Monocular (Best Corrected) and Binocular (Uncorrected and Best Corrected) Distance Visual Acuity

- There were no clinically relevant differences in the mean monocular BCDVA at 12 months (Visit 5) for subjects implanted with the ReSTOR Toric IOL (0.02 ± 0.10 logMAR in the first eye and 0.01 ± 0.10 logMAR in the second eye) compared with subjects implanted with the Control IOL (0.02 ± 0.12 logMAR in the first eye and 0.01 ± 0.10 logMAR in the second eye).
- There were no clinically relevant differences in the mean binocular UCDVA between the ReSTOR Toric IOL (0.03 ± 0.11 logMAR) and the Control IOL (0.02 ± 0.10 logMAR) at 12 months (Visit 5)
- There were no clinically relevant differences in the mean binocular BCDVA at 12 months (Visit 5) for subjects implanted with the ReSTOR Toric IOL (-0.04 ± 0.09 logMAR) compared with subjects implanted with the Control IOL (-0.04 ± 0.08 logMAR).

Monocular (Distance Corrected for Optical Infinity and Best Corrected) and Binocular (Uncorrected, Distance Corrected for optical infinity and Best Corrected) Near Visual Acuity at Fixed Distance

- No clinically relevant differences in mean monocular DCNVA at Fixed Distance were observed between the ReSTOR Toric IOL (0.15 ± 0.14logMAR for the first eye and 0.15 ± 0.14 logMAR in the second eye) and the Control IOL (0.18 ± 0.16 logMAR in the first eye and 0.18 ± 0.15 logMAR in the second eye) at 12 months (Visit 5).
- No clinically relevant differences in mean monocular BCNVA at Fixed Distance were observed between the ReSTOR Toric IOL (0.11 ± 0.13 logMAR for the first eye and 0.10 ± 0.14 logMAR in the second eye) and the Control IOL (0.14 ± 0.16 logMAR in the first eye and 0.14 ± 0.14 logMAR in the second eye) at 12 months (Visit 5).
- No clinically relevant differences in the mean binocular UCNVA at Fixed Distance were observed between the ReSTOR Toric IOL and the (0.10 ± 0.13 logMAR) and the Control IOL (0.14 ± 0.13 logMAR) at 12 months (Visit 5).
- No clinically relevant differences in mean binocular DCNVA at Fixed Distance were observed between the ReSTOR Toric IOL (0.08 ± 0.11 logMAR) and the Control IOL (0.11 ± 0.12 logMAR) at 12 months (Visit 5).
- No clinically relevant differences in mean binocular BCNVA at Fixed Distance were observed between the ReSTOR Toric IOL (0.04 ± 0.11 logMAR) and the Control IOL (0.07 ± 0.11 logMAR) at 12 months (Visit 5).

Monocular and Binocular Near Visual Acuity at Best Distance: Uncorrected and Distance Corrected for Optical Infinity

- No clinically relevant differences in mean monocular UCNVA at Best Distance were observed between the ReSTOR Toric IOL (0.17 ± 0.14 logMAR in the first eye and 0.16 ± 0.14 logMAR in

the second eye) and the Control IOL (0.19 ± 0.17 logMAR in the first eye and 0.18 ± 0.16 logMAR in the second eye) at 12 months (Visit 5).

- No clinically relevant differences in mean monocular DCNVA at Best Distance were observed between the ReSTOR Toric IOL (0.14 ± 0.13 logMAR for the first eye and 0.14 ± 0.13 logMAR in the second eye) and the Control IOL (0.15 ± 0.15 logMAR in the first eye and 0.14 ± 0.14 logMAR in the second eye) at 12 months (Visit 5).
- No clinically relevant differences in mean binocular UCNVA at Best Distance (0.09 ± 0.11 logMAR) and the Control IOL (0.11 ± 0.12 logMAR) at 12 months (Visit 5).
- No clinically relevant differences in mean binocular DCNVA at Best Distance were observed between the ReSTOR Toric IOL (0.08 ± 0.11 logMAR) and the Control IOL (0.09 ± 0.11 logMAR) at 12 months (Visit 5).

Monocular and Binocular Mesopic Near Visual Acuity at Best Distance: Distance Corrected for Optical Infinity

- No clinically relevant differences in mean monocular mesopic DCNVA at Best Distance were observed between the ReSTOR Toric IOL (0.44 ± 0.24 logMAR for the first eye and 0.43 ± 0.23 logMAR in the second eye) and the Control IOL (0.49 ± 0.25 logMAR in the first eye and 0.50 ± 0.25 logMAR in the second eye) at 12 months (Visit 5).
- No clinically relevant differences in mean binocular mesopic DCNVA at Best Distance were observed between the ReSTOR Toric IOL (0.32 ± 0.19 logMAR) and the Control IOL (0.37 ± 0.22 logMAR) at 12 months (Visit 5).

There were 5 subjects with monocular UCDVA worse than 20/63 and monocular BCDVA worse than 20/40 at study Visits 3, 4, or 5, indicating that residual refractive error was not the only contributor to their monocular UCDVA of 20/63 or worse. None of these outcomes were attributed to the ReSTOR Toric or Control IOL, and possible alternative etiology and/or ocular pathology were identified for all 5 subjects, which are discussed in Appendix 1.

3.5.1.3 Intermediate Visual Acuity

At all 3 intermediate testing distances (50 cm, 60 cm, and 70 cm), the mean binocular uncorrected intermediate visual acuity (UCIVA) for the ReSTOR Toric IOL compared favorably to the Control IOL; the ReSTOR Toric IOL subjects had approximately 1 line better VA (mean VA lower by ≥ 0.1 logMAR). At 12 months (Visit 5), the observed difference in UCIVA between lens models favored the ReSTOR Toric IOL at all distances, with the greatest observed difference being 1.5 lines at 50 cm and 60 cm (Table 17). A higher percentage of ReSTOR Toric IOL subjects achieved binocular UCIVA of 20/40 or better at the test distances of 50 cm, 60 cm, and 70 cm compared to Control IOL control subjects at 12 months (Visit 5) (Table 18). This is expected as the shift in the near reading distance from the +4.0 D Control IOL (33 cm) to the +3.0 D ReSTOR Toric IOL (40 cm) improves vision at intermediate distances.

Table 17. Descriptive Statistics for Binocular Uncorrected Intermediate Visual Acuity at 12 Months (Visit 5) (All Implanted Population)

		ReSTOR Toric IOL	Control IOL
VA at 50 cm	n	371	180
	Mean (SD)	0.13 (0.14)	0.28 (0.17)
	(Min, Max)	(-0.20, 0.60)	(-0.18, 0.74)
	95% CI	(0.11, 0.14)	(0.26, 0.31)
VA at 60 cm	n	371	180
	Mean (SD)	0.17 (0.15)	0.32 (0.15)
	(Min, Max)	(-0.26, 0.54)	(-0.24, 0.64)
	95% CI	(0.16, 0.19)	(0.29, 0.34)
VA at 70 cm	n	371	180
	Mean (SD)	0.21 (0.14)	0.32 (0.15)
	(Min, Max)	(-0.30, 0.68)	(-0.22, 0.76)
	95% CI	(0.19, 0.22)	(0.29, 0.34)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3

Table 18. Number and Percentage of Subjects with Binocular Uncorrected Intermediate Visual Acuity at 12 Months (Visit 5) (All Implanted Population)

		ReSTOR Toric IOL		Control IOL	
VA at 50 cm	n	371		180	
	20/40 or better	346	(93.3)	114	(63.3)
	Worse than 20/40	25	(6.7)	66	(36.7)
VA at 60 cm	n	371		180	
	20/40 or better	320	(86.3)	85	(47.2)
	Worse than 20/40	51	(13.7)	95	(52.8)
VA at 70 cm	n	371		180	
	20/40 or better	296	(79.8)	91	(50.6)
	Worse than 20/40	75	(20.2)	89	(49.4)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3

Additionally, clinically relevant differences favoring the ReSTOR Toric IOL were also observed for mean Distance Corrected Intermediate Visual Acuity at all testing distances (50 cm, 60 cm, and 70 cm).

In Clinical Study C-09-036 a difference in visual acuity up to 1.5 lines (0.15 logMAR) in favor of the ReSTOR Toric IOL at all 3 intermediate distances (50, 60 and 70 cm) was observed indicating improved cumulative binocular distance-corrected visual acuity across distances (near at best distance, intermediate at 50 cm, and distance). Alcon believes that the design of the lower add power (+3.0 D) of

the ReSTOR Toric IOL contributed to the improved intermediate VA at 50 cm and led to a higher observed percentage of subjects that achieved ≥20/20, ≥20/25, ≥20/32, and ≥20/40 binocular uncorrected or distance corrected visual acuities when combining distance, intermediate at 50 cm, and near vision results at 12 months (Visit 5) as compared to the parent control ReSTOR +4.0 D add power IOL.

3.5.1.4 Sensitivity Analyses for Uncorrected Distance and Near Visual Acuity

Overall, there were minimal missing data in Clinical Study C-09-036 as summarized in Table 19. For the first implanted eye, 19 of 574 subjects were missing UCDVA data at 12 months (Visit 5) with little difference between groups. Missing data rates were similar for the second implanted eye and for UCNVA.

Table 19. Summary of Available Data for Sensitivity Analyses (All Implanted Population)

	ReSTOR Toric IOL	Control IOL
UCDVA		
First Implanted Eye		
Total	386	188
Visit 5 data available	373	182
Visit 5 data unavailable; other post implant data available	13	6
No post implant data available	0	0
Second Implanted Eye		
Total	382	188
Visit 5 data available	371	182
Visit 5 data unavailable; other post implant data available	11	6
No post implant data available	0	0
UCNVA		
First Implanted Eye		
Total	386	188
Visit 5 data available	373	182
Visit 5 data unavailable; other post implant data available	11	5
No post implant data available	2	1
Second Implanted Eye		
Total	382	188
Visit 5 data available	371	182
Visit 5 data unavailable; other post implant data available	11	5
No post implant data available	0	1

Source: Table 32-1 and Table 32-2 in Deficiency Response.
ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
UCDVA = Uncorrected Distance Visual Acuity
UCNVA = Uncorrected Near Visual Acuity at Fixed Distance

To evaluate the impact of missing data, two sensitivity analyses were conducted. Prespecified method 1 used repeated measures ANCOVA with imputation of the median of all values for that subject when

missing a 12-month value. Subjects with no postoperative data could not be included for method 1 resulting in exclusion of 3 subjects for sensitivity analysis of UCNVA in the first eye, and exclusion of 1 subject in the sensitivity analysis of UCNVA in the second eye. The findings for UCDVA (Table 20 and Table 21) and UCNVA (Table 22 and Table 23) were consistent with the primary analysis.

Table 20. Comparison of Monocular Uncorrected Distance Visual Acuity at 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 1, First Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=386)	Control IOL (N=188)	Difference (95%UCL)
First Implanted Eye	Mean	0.128	0.127	0.001 (0.029)
	SE	0.012	0.015	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on the repeated measure analysis of covariance
UCL = 95% Upper confidence limit; SE = Standard error

Table 21. Comparison of Monocular Uncorrected Distance Visual Acuity at 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 1, Second Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=382)	Control IOL (N=188)	Difference (95%UCL)
Second Implanted Eye	Mean	0.116	0.104	0.012 (0.040)
	SE	0.011	0.013	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on the repeated measure analysis of covariance
UCL = 95% Upper confidence limit; SE = Standard error

Table 22. Comparison of Monocular Uncorrected Near Visual Acuity at Fixed Distance At 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 1, First Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=384)	Control IOL (N=187)	Difference (95%UCL)
First Implanted Eye	Mean	0.193	0.240	-0.047 (-0.021)
	SE	0.015	0.017	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
ReSTOR IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on analysis of covariance.
UCL = 95% Upper confidence limit; SE = Standard error

Table 23. Comparison of Monocular Uncorrected Near Visual Acuity at Fixed Distance At 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 1, Second Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=382)	Control IOL (N=187)	Difference (95%UCL)
Second Implanted Eye	Mean	0.182	0.239	-0.056 (-0.030)
	SE	0.013	0.015	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
ReSTOR IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on analysis of covariance.
UCL = 95% Upper confidence limit; SE = Standard error

Prespecified method 2 also used repeated measures ANCOVA but with imputation of the worst value from all subjects treated with the ReSTOR Toric IOL if a subject treated with ReSTOR Toric was missing data at 12 months (Visit 5). In the Control IOL treatment group, a subject missing data at 12 months (Visit 5) had imputation of best value from subjects in the Control IOL treatment group. All subjects in the All Implanted analysis population were included with this method. The findings for UCDVA (Table 24 and Table 25) and UCNVA (Table 26 and Table 27) were also consistent with the primary analysis.

Table 24. Comparison of Monocular Uncorrected Distance Visual Acuity at 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 2, First Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=386)	Control IOL (N=188)	Difference (95%UCL)
First Implanted Eye	Mean	0.153	0.112	0.040 (0.069)
	SE	0.016	0.019	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on the repeated measure analysis of covariance
UCL = 95% Upper confidence limit; SE = Standard error

Table 25. Comparison of Monocular Uncorrected Distance Visual Acuity at 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 2, Second Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=382)	Control IOL (N=188)	Difference (95%UCL)
Second Implanted Eye	Mean	0.138	0.089	0.049 (0.076)
	SE	0.012	0.015	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL - Control IOL
Estimates were based on the repeated measure analysis of covariance
UCL = 95% Upper confidence limit; SE = Standard error

Table 26. Comparison of Monocular Uncorrected Near Visual Acuity at Fixed Distance At 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 2, First Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=386)	Control IOL (N=188)	Difference (95%UCL)
First Implanted Eye	Mean	0.211	0.223	-0.012 (0.014)
	SE	0.016	0.018	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL – Control IOL
Estimates were based on analysis of covariance.
UCL = 95% Upper confidence limit; SE = Standard error

Table 27. Comparison of Monocular Uncorrected Near Visual Acuity at Fixed Distance At 12 Months (Visit 5) Using Least Squares Estimates Imputation Method 2, Second Implanted Eye (All Implanted Population)

		ReSTOR Toric IOL (N=382)	Control IOL (N=188)	Difference (95%UCL)
Second Implanted Eye	Mean	0.198	0.220	-0.022 (0.005)
	SE	0.013	0.016	

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Difference = ReSTOR Toric IOL – Control IOL
Estimates were based on analysis of covariance.
UCL = 95% Upper confidence limit; SE = Standard error

All 95% UCL findings met the clinical performance target of 0.1 logMAR. Therefore, overall, the findings from the 2 prespecified methods to evaluate the role of missing data were consistent with the primary analysis

3.5.1.5 Categorical Snellen Visual Acuity at 12 Months (Visit 5)

Supportive analyses were also conducted to examine categorical Snellen visual acuity at 12 months (Visit 5). The findings indicate that both the ReSTOR Toric IOL and the Control IOL achieved desired visual performance for near, intermediate, and distance vision. Results for UCDVA and UCNVA at fixed distance are shown at 12 months (Visit 5) in Table 28 and Table 29 for the percentage of subjects achieving 20/40 or better visual acuity. For UCDVA, more than 90% in both treatment groups achieved 20/40 visual acuity or greater in both eyes. For UCNVA at fixed distance, at least 80% of subjects in both treatment groups achieved 20/40 visual acuity or greater in both eyes.

Table 28. UCDVA: Percentage of Patients with 20/40 or better Snellen Acuity at 12 Months (Visit 5) (All Implanted Population)

		First Implanted Eye				Second Implanted Eye			
		ReSTOR Toric IOL		Control IOL		ReSTOR Toric IOL		Control IOL	
		n	%	n	%	n	%	n	%
Visit 5	Total	373		180		371		180	
	20/40 or better	344	(92.2)	167	(92.8)	348	(93.8)	175	(97.2)
	Worse than 20/40	29	(7.8)	13	(7.2)	23	(6.2)	5	(2.8)

Table 29. UCNVA at fixed distance: Percentage of Patients with 20/40 or better Snellen Acuity at 12 Months (Visit 5) (All Implanted Population)

		First Implanted Eye				Second Implanted Eye			
		ReSTOR Toric IOL		Control IOL		ReSTOR Toric IOL		Control IOL	
		n	%	n	%	n	%	n	%
Visit 5	Total	373		180		371		180	
	20/40 or better	323	(86.6)	144	(80.0)	319	(86.0)	145	(80.6)
	Worse than 20/40	50	(13.4)	36	(20.0)	52	(14.0)	35	(19.4)

3.5.1.6 Uncorrected Distance and Near Visual Acuity by Investigative Site

UCDVA findings by investigative site are illustrated in Figure 13 and those for UCNVA at fixed distance in Figure 14 in the first eye. For both UCDVA and UCNVA, the majority of sites experienced findings that favored ReSTOR Toric. Findings for the second eye were similar (not shown) supporting the robustness of the findings for visual acuity.

Figure 13. Difference between Treatment Groups in Monocular Uncorrected Distance Visual Acuity at 12 Months (Visit 5) by Investigator (First Eye - All Implanted Population)

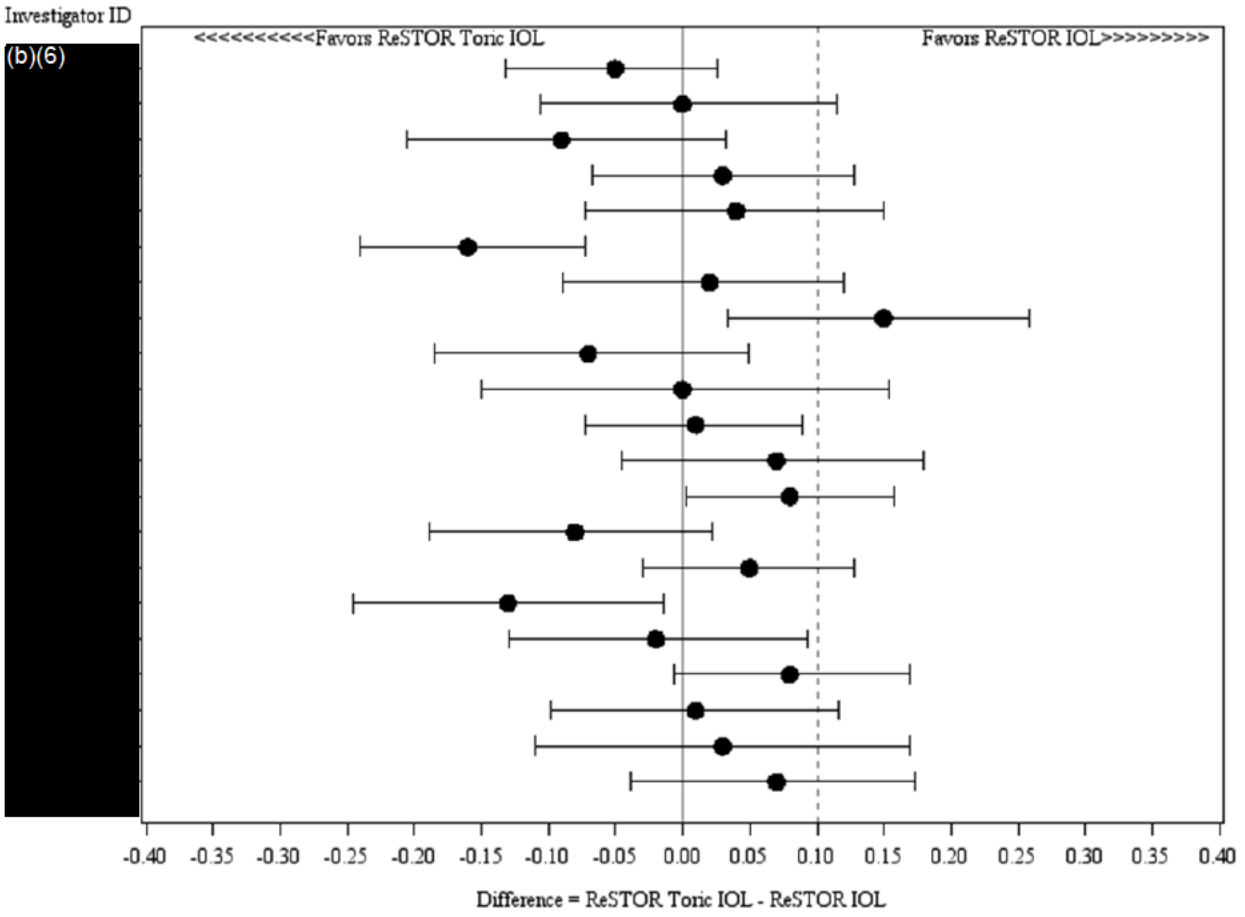
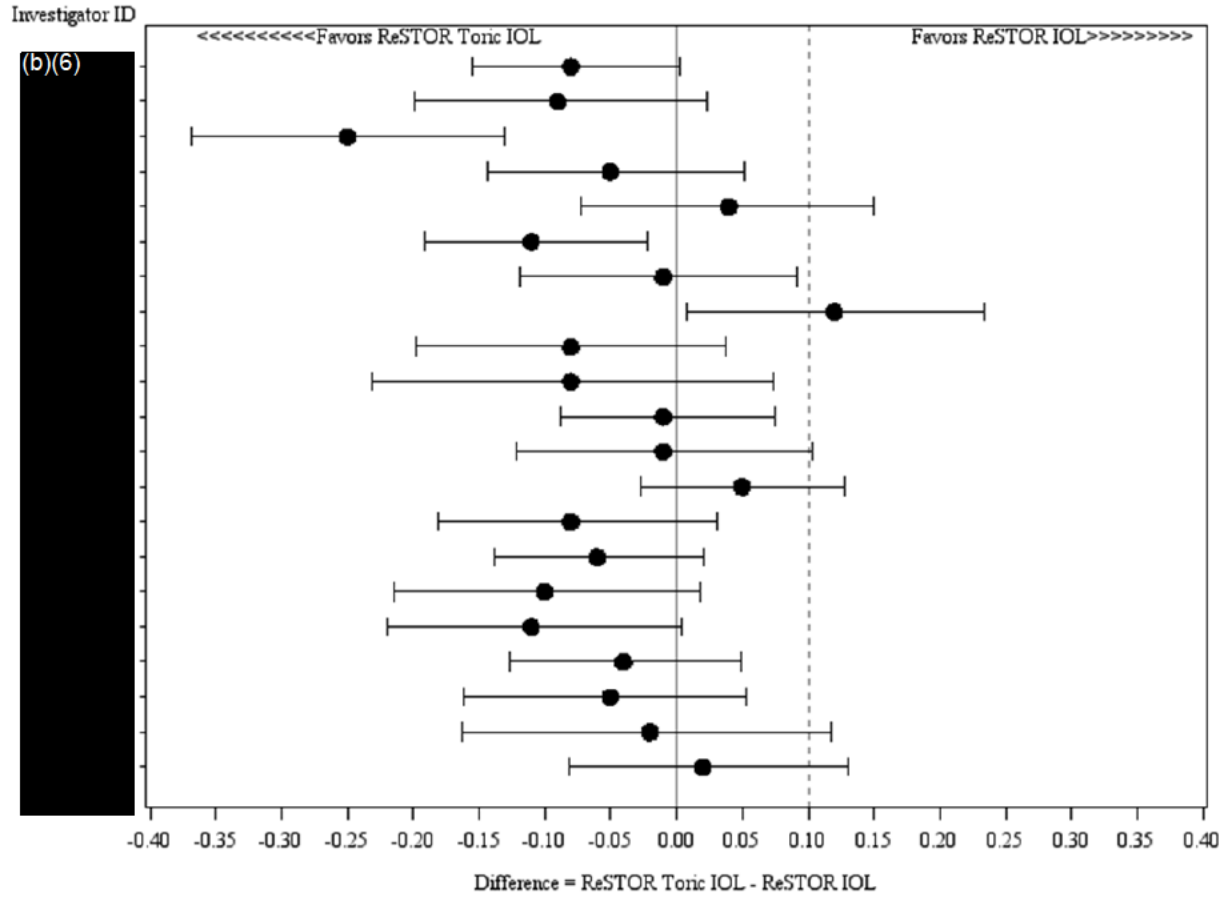


Figure 14. Difference in Monocular Uncorrected Near Visual Acuity at Fixed Distance at 12 Months (Visit 5) by Investigator (First Eye - All Implanted Population)



3.5.2 Misalignment

Misalignment refers to the difference between the intended placement position (calculated using preoperative biometry measurements and the study specific web-based Alcon IQ ReSTOR Multifocal Toric IOL Clinical Calculator) and the observed position at a subsequent visit. In this study, a custom software "Photographic Assessment of Lens Orientation (PALO)" was used to measure toric IOL orientation. The PALO software allowed the operator to select the toric lens markers and anatomical landmarks on the eye and use their coordinate locations to yield a quantitative measure of the axis of orientation of the implanted IOL. This 21 CFR Part 11 compliant software was validated in a clinical setting for reliability and repeatability.

Accuracy of lens placement was demonstrated in Clinical Study C-09-036 with the mean absolute difference between intended axis orientation and achieved axis orientation at surgery being 5.0° ± 6.1° for the ReSTOR Toric IOL in the first operative eyes.

3.5.3 Rotational Stability

Rotation is the change from the IOL orientation achieved at surgery and the observed orientation at a subsequent visit. In the ReSTOR Toric IOL group from surgery to 12 months (Visit 5), 97.2% of first and second eyes had less than 10 degrees of rotation. The mean absolute difference between the achieved lens axis orientation at surgery and at 12 months (Visit 5) was 2.7° ± 5.8° in the first operative eyes and 2.2° ± 2.7° in the second operative eyes (Table 30). Furthermore, the mean actual (either positive or negative) difference between the achieved lens axis orientation and the achieved axis placement at surgery was ≤ 1.0° ± 6.3° in the first and second operative eyes at all postoperative visits.

Table 30. Descriptive Statistics for the Difference Between Lens Axis Orientation at the Postoperative Visit and Achieved Axis Placement (Degrees) at the Operative Visit (All Implanted Population)

		Absolute Rotation		Actual Rotation	
		First Implanted Eye	Second Implanted Eye	First Implanted Eye	Second Implanted Eye
Visit 1	N	376	375	376	375
	Mean (SD)	1.4 (1.8)	1.5 (1.7)	-0.1 (2.3)	-0.0 (2.2)
	(Min, Max)	(0, 18)	(0, 14)	(-11, 18)	(-6, 14)
	95% CI	(1.2, 1.6)	(1.3, 1.6)	(-0.3, 0.2)	(-0.2, 0.2)
Visit 2	N	375	366	375	366
	Mean (SD)	1.8 (2.3)	2.0 (2.7)	0.5 (2.9)	0.6 (3.3)
	(Min, Max)	(0, 23)	(0, 30)	(-11, 23)	(-23, 30)
	95% CI	(1.6, 2.0)	(1.7, 2.2)	(0.2, 0.8)	(0.2, 0.9)
Visit 3	N	367	368	367	368
	Mean (SD)	2.2 (5.1)	2.1 (2.7)	0.8 (5.5)	0.9 (3.3)
	(Min, Max)	(0, 85)	(0, 24)	(-17, 85)	(-24, 24)
	95% CI	(1.6, 2.7)	(1.8, 2.4)	(0.3, 1.4)	(0.6, 1.3)
Visit 4	N	363	364	363	364
	Mean (SD)	2.3 (5.2)	2.3 (3.0)	1.0 (5.6)	1.0 (3.6)
	(Min, Max)	(0, 85)	(0, 27)	(-13, 85)	(-24, 27)
	95% CI	(1.7, 2.8)	(2.0, 2.6)	(0.4, 1.6)	(0.7, 1.4)
Visit 5	N	356	357	356	357
	Mean (SD)	2.7 (5.8)	2.2 (2.7)	1.0 (6.3)	0.7 (3.4)
	(Min, Max)	(0, 84)	(0, 24)	(-36, 84)	(-24, 19)
	95% CI	(2.1, 3.3)	(1.9, 2.5)	(0.4, 1.7)	(0.4, 1.1)

For subjects with missing Operative Visit axis placement data, Day 1 (Visit 1) data were used as baseline

A post-hoc analysis was also performed to confirm that the rotational stability of the ReSTOR Toric IOL was maintained between 2 consecutive visits at least 3 months apart (between Visits 3 and 4), as specified by the 2010 ANSI standard for toric intraocular lenses. The data demonstrate that 94.2% (first eye) and 93.9% (second eye) of ReSTOR Toric IOL subjects achieved a rotational stability of 5 degrees or less between 2 consecutive visits, at least 3 months apart (Visits 3 and 4).

3.5.4 Reduction of Cylinder

The ReSTOR Toric IOL was designed to correct preexisting corneal astigmatism by reducing or eliminating this refractive cylinder. In this study, the ReSTOR Toric IOL subjects were required to have preoperative corneal astigmatism of ≥ 0.75 D, measured by the IOLMaster optical biometry instrument (Carl Zeiss Meditec, Inc., Dublin, California) in both operative eyes and 0.75 D to 2.82 D of predicted crossed cylinder in both operative eyes, calculated by the study specific web-based ReSTOR Toric Clinical Calculator for the ReSTOR Toric IOL Models SND1T3- SND1T6.

The percent reduction in cylinder with respect to target cylinder was calculated, and descriptive statistics were computed at each postoperative visit. Target cylinder was defined as the amount of anticipated residual corneal astigmatism as calculated by the ReSTOR Toric Clinical Calculator.

The ReSTOR Toric IOL was effective in reducing astigmatism in subjects with preexisting corneal astigmatism. As presented in Table 31, subjects implanted with the ReSTOR Toric IOL demonstrated a mean percent reduction in cylinder with respect to target cylinder of at least 76.6% in the first and second operative eyes at all postoperative visits. Similarly, 74.5% of subjects implanted with the ReSTOR Toric IOL achieved a reduction in astigmatism to within 0.5 D of the target cylinder, and 94.1% of subjects achieved a reduction to within 1.0 D of the target cylinder, in the first 12 months (Table 32). Similar results were obtained when the ReSTOR Toric IOL was analyzed by lens models SND1T3/SND1T4 and SND1T5/SND1T6 separately (Table 33).

Table 31. Descriptive Statistics for Percent Reduction in Cylinder With Respect to Target Cylinder (All Implanted Population)

		First Implanted Eye	Second Implanted Eye	Overall
Visit 1	n	386	382	768
	Mean (SD)	86.5 (28.0)	85.7 (33.6)	86.1 (30.9)
	(Min, Max)	(-49, 137)	(-43, 160)	(-49, 160)
	95% CI	(83.7, 89.3)	(82.3, 89.0)	(83.9, 88.3)
Visit 2	n	386	382	768
	Mean (SD)	84.8 (28.2)	86.5 (36.0)	85.6 (32.3)
	(Min, Max)	(-45, 155)	(-133, 160)	(-133, 160)
	95% CI	(82.0, 87.6)	(82.9, 90.1)	(83.4, 87.9)
Visit 3	n	383	382	765
	Mean (SD)	83.3 (28.4)	84.2 (32.1)	83.8 (30.3)
	(Min, Max)	(-34, 155)	(-69, 160)	(-69, 160)
	95% CI	(80.5, 86.2)	(80.9, 87.4)	(81.6, 85.9)
Visit 4	n	379	377	756
	Mean (SD)	81.7 (29.0)	78.0 (35.1)	79.9 (32.2)
	(Min, Max)	(-37, 155)	(-84, 160)	(-84, 160)
	95% CI	(78.8, 84.6)	(74.5, 81.6)	(77.6, 82.2)
Visit 5	n	373	371	744
	Mean (SD)	77.6 (31.1)	76.6 (36.8)	77.1 (34.0)
	(Min, Max)	(-63, 155)	(-118, 151)	(-118, 155)
	95% CI	(74.5, 80.8)	(72.9, 80.4)	(74.7, 79.6)

Table 32. Number and Percentage of Subjects with Reduction of Cylinder within the Target Cylinder Correction Categories (All Implanted Population)

		First Implanted Eye		Second Implanted Eye	
		n	(%)	n	(%)
Visit 1	Total	386		382	
	Within 0.5D	331	(85.8)	325	(85.1)
	Within 1.0D	376	(97.4)	379	(99.2)
	> 1.0D	10	(2.6)	3	(0.8)
Visit 2	Total	386		382	
	Within 0.5D	316	(81.9)	329	(86.1)
	Within 1.0D	374	(96.9)	378	(99.0)
	> 1.0D	12	(3.1)	4	(1.0)
Visit 3	Total	383		382	
	Within 0.5D	304	(79.4)	339	(88.7)
	Within 1.0D	369	(96.3)	378	(99.0)
	> 1.0D	14	(3.7)	4	(1.0)
Visit 4	Total	379		377	
	Within 0.5D	301	(79.4)	302	(80.1)
	Within 1.0D	366	(96.6)	370	(98.1)
	> 1.0D	13	(3.4)	7	(1.9)
Visit 5	Total	373		371	
	Within 0.5D	278	(74.5)	295	(79.5)
	Within 1.0D	351	(94.1)	362	(97.6)
	> 1.0D	22	(5.9)	9	(2.4)

Table 33. Number and Percentage of Subjects with Reduction of Cylinder within the Target Cylinder Correction Categories by Lens Model (All Implanted Population)

		First Implanted Eye				Second Implanted Eye			
		SND1T3/ SNDIT4		SND1T5/ SND1T6		SND1T3/ SND1T4		SND1T5/ SND1T6	
		n	(%)	n	(%)	n	(%)	n	(%)
Visit 1	Total	269		117		316		66	
	Within 0.5D	231	(85.9)	100	(85.5)	268	(84.8)	57	(86.4)
	Within 1.0D	262	(97.4)	114	(97.4)	314	(99.4)	65	(98.5)
	> 1.0D	7	(2.6)	3	(2.6)	2	(0.6)	1	(1.5)
Visit 2	Total	269		117		316		66	
	Within 0.5D	229	(85.1)	87	(74.4)	275	(87.0)	54	(81.8)
	Within 1.0D	262	(97.4)	112	(95.7)	312	(98.7)	66	(100.0)
	> 1.0D	7	(2.6)	5	(4.3)	4	(1.3)	0	(0.0)
Visit 3	Total	267		116		316		66	
	Within 0.5D	222	(83.1)	82	(70.7)	282	(89.2)	57	(86.4)
	Within 1.0D	260	(97.4)	109	(94.0)	312	(98.7)	66	(100.0)
	> 1.0D	7	(2.6)	7	(6.0)	4	(1.3)	0	(0.0)
Visit 4	Total	265		114		311		66	
	Within 0.5D	222	(83.8)	79	(69.3)	249	(80.1)	53	(80.3)
	Within 1.0D	257	(97.0)	109	(95.6)	306	(98.4)	64	(97.0)
	> 1.0D	8	(3.0)	5	(4.4)	5	(1.6)	2	(3.0)
Visit 5	Total	260		113		306		65	
	Within 0.5D	206	(79.2)	72	(63.7)	244	(79.7)	51	(78.5)
	Within 1.0D	248	(95.4)	103	(91.2)	299	(97.7)	63	(96.9)
	> 1.0D	12	(4.6)	10	(8.8)	7	(2.3)	2	(3.1)

3.5.5 Binocular Defocus

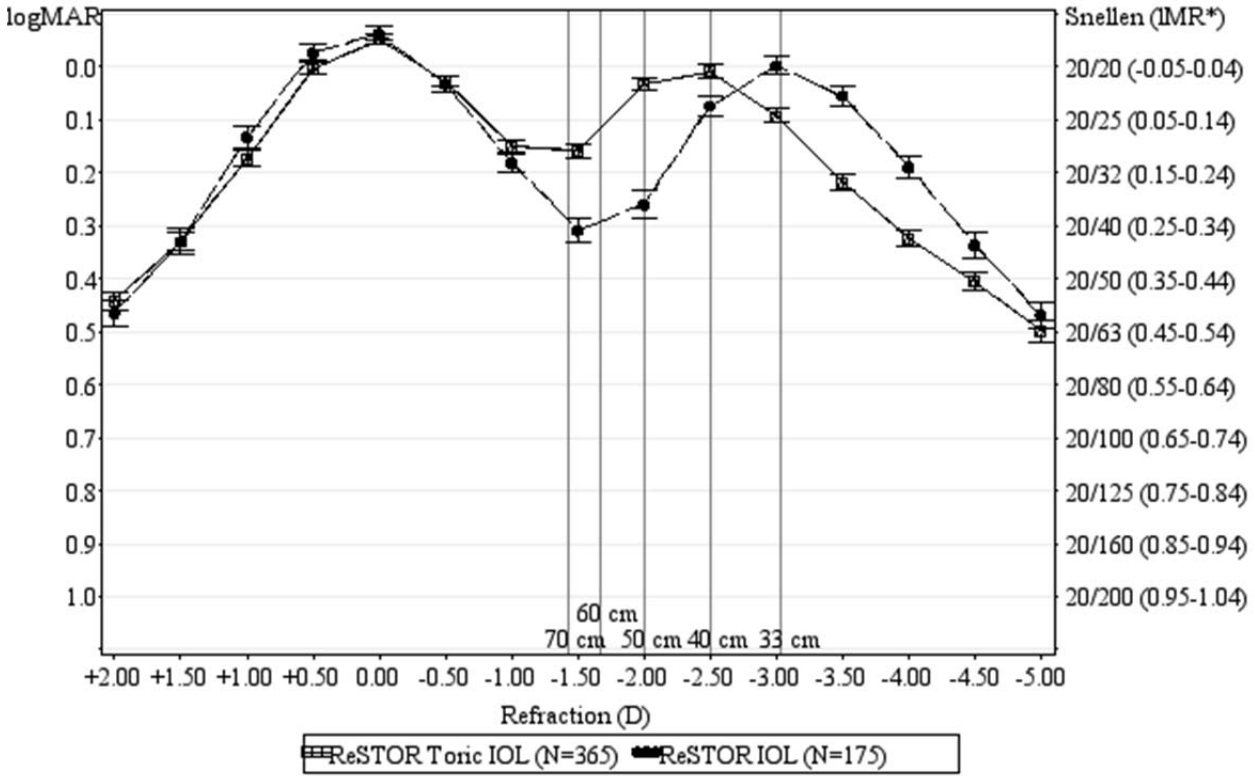
Binocular defocus curves (depth of focus data) provide a measure of distance corrected binocular visual acuity in the presence of varying amounts of spherical defocus. These data were captured during Visit 4 (120-180 days after second eye implant) to evaluate the performance of the ReSTOR Toric IOL, when implanted bilaterally, and compared to the control ReSTOR IOL. Binocular defocus testing was performed using either a phoropter or trial frames and a 100% contrast ETDRS chart positioned 4 meters from the subject under photopic lighting conditions. The manifest refraction for each subject was used to designate the zero baseline. To begin the testing, subjects were defocused by -5.00 D of spherical power from their best distance correction (manifest refraction). The logMAR visual acuity at this refractive state was recorded. The negative spherical power was decreased in 0.50 D increments (i.e., subjects were defocused by -4.50 D, -4.00 D, -3.50 D, …, -0.50 D, 0.00 D from their manifest distance refraction), and logMAR visual acuity was recorded at each defocus power, until only the best distance correction (manifest refraction) remained. Next, subjects were defocused by +2.00 D of spherical power from their best distance correction (manifest refraction) and their logMAR visual acuity was recorded. The positive spherical power was decreased in 0.5 D increments (i.e., subjects were defocused by +1.50 D, +1.00 D, +0.50 D from their manifest distance refraction), and logMAR visual acuity was recorded at each change in defocus power, until only the best distance correction (manifest refraction) remained.

Defocus curves obtained in each treatment group at Visit 4 are presented in Figure 15 (defocus curves are assessed using the best case study population as per ISO 11979-9:2006). In general, the curves were similar between treatment groups. Binocular intermediate vision at 1.25 - 1.5 D was elevated approximately 1.5 lines (0.15 logMAR) with the ReSTOR Toric IOL which was attributable to its lower add power (+3.0 D for the RESTOR Toric and +4.0 D for the Control IOL).

Subjects implanted with the ReSTOR Toric IOL achieved mean 20/32 or better vision (depth of focus) over near, intermediate and distance (28 cm and beyond). Expanded depth of focus is more pronounced at near distance. As expected, a shift in the near peak of the defocus curve was observed, with peak near vision for the ReSTOR Toric IOL at -2.5 D (which corresponds to an equivalent distance of 40 cm) of defocus compared to -3.0 D (which corresponds to an equivalent distance of 33 cm) of defocus for the Control IOL, which were the design distances for each lens.

In summary, ReSTOR Toric IOL provides functional vision (20/32 or better) over near, intermediate and distance.

Figure 15. Mean Defocus Curves by Treatment Group at Visit 4 (Best Case Population)



ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
ReSTOR IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
*lMR = logMAR Range

3.5.6 Contrast Sensitivity

Contrast Sensitivity testing was conducted using the CSV-1000E chart (VectorVision Inc., Greenville, OH) under photopic (well-lit conditions, at least 85 cd/m^2) and mesopic (low light, approximately 3 cd/m^2) conditions without and with a glare source. The CSV-1000E chart used distance sine-wave gratings at 9 contrast levels and incorporated a self-calibrating retro-illuminated test face maintaining a light level of 85 cd/m2. Testing was performed at 8 feet with best spectacle correction in place for each of 4 spatial frequencies. For photopic conditions, subjects were tested at the spatial frequencies of 3, 6, 12 and 18 cycles per degree (cpd), as per ISO 11979-9:2006. For mesopic conditions, subjects were tested at the spatial frequencies of 1.5, 3, 6 and 12 cpd, as per ISO 11979-9:2006, using a neutral density filter to reduce the effective chart luminance to approximately 3 cd/m2. Prior to mesopic contrast sensitivity testing, subjects were dark adapted for 10 minutes in an examination room with the lights turned off and viewing the illuminated contrast sensitivity chart with neutral density filters placed in a plastic frame. The last correct response at each spatial frequency was recorded as the contrast sensitivity threshold. Treatment group comparisons between the ReSTOR Toric IOL and the control ReSTOR IOL for

contrast sensitivity were evaluated for photopic and mesopic lighting conditions without and with glare using "Best Case" subjects. For comparisons made between the treatment groups, a clinical performance target was defined as a difference in contrast sensitivity of 0.15 log units (based upon the ISO standard (IS0 11979-9: 2006).

Mean binocular photopic contrast sensitivity was similar between the ReSTOR Toric IOL and the Control IOL without and with a glare source (Table 34). All observed differences in means between the ReSTOR Toric IOL and the Control IOL were smaller than or equal to 0.05 log units (0.05 difference between means was observed for the spatial frequency of 6 cpd at Visit 4).

Table 34. Binocular Distance Photopic Contrast Sensitivity at Visit 4 (Best Case Population)

		Photopic Without Glare		Photopic With Glare	
		ReSTOR Toric IOL	Control IOL	ReSTOR Toric IOL	Control IOL
3.0 CPD	n	360	173	360	173
	Mean (SD)	1.68 (0.22)	1.71 (0.23)	1.59 (0.27)	1.62 (0.28)
	(Min, Max)	(1.18, 2.08)	(0.70, 2.08)	(0.40, 2.08)	(0.40, 2.08)
	95% CI	(1.65, 1.70)	(1.67, 1.74)	(1.56, 1.61)	(1.58, 1.66)
6.0 CPD	n	360	173	360	173
	Mean (SD)	1.78 (0.24)	1.81 (0.23)	1.61 (0.39)	1.66 (0.36)
	(Min, Max)	(0.61, 2.29)	(0.90, 2.29)	(0.61, 2.29)	(0.61, 2.29)
	95% CI	(1.76, 1.81)	(1.78, 1.85)	(1.57, 1.65)	(1.61, 1.71)
12.0 CPD	n	360	173	360	173
	Mean (SD)	1.38 (0.35)	1.37 (0.32)	1.25 (0.41)	1.24 (0.38)
	(Min, Max)	(0.31, 2.00)	(0.31, 2.00)	(0.31, 2.00)	(0.31, 2.00)
	95% CI	(1.34, 1.42)	(1.32, 1.42)	(1.21, 1.29)	(1.18, 1.30)
18.0 CPD	n	360	173	360	173
	Mean (SD)	0.87 (0.31)	0.88 (0.30)	0.84 (0.33)	0.81 (0.32)
	(Min, Max)	(-0.13, 1.56)	(-0.13, 1.56)	(-0.13, 1.56)	(-0.13, 1.56)
	95% CI	(0.84, 0.90)	(0.83, 0.92)	(0.80, 0.87)	(0.77, 0.86)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3

Mean contrast sensitivity scores were similar between the ReSTOR Toric IOL and the Control IOL for both mesopic lighting conditions without and with a glare source with the greatest difference of 0.03 log units found for the spatial frequency of 12 cpd at Visit 4 (Table 35).

Table 35. Descriptive Statistics for Binocular Distance Mesopic Contrast Sensitivity at Visit 4 (Best Case Population)

		Mesopic without glare		Mesopic with glare	
		ReSTOR Toric IOL	Control IOL	ReSTOR Toric IOL	Control IOL
1.5 CPD	n	359	172	359	172
	Mean (SD)	1.57 (0.26)	1.55 (0.25)	1.51 (0.29)	1.50 (0.28)
	(Min, Max)	(0.30, 1.97)	(0.30, 1.97)	(0.30, 1.97)	(0.30, 1.97)
	95% CI	(1.54, 1.59)	(1.51, 1.59)	(1.48, 1.54)	(1.46, 1.55)
3.0 CPD	n	360	172	360	172
	Mean (SD)	1.57 (0.25)	1.57 (0.24)	1.55 (0.28)	1.55 (0.26)
	(Min, Max)	(0.70, 2.08)	(0.85, 2.00)	(0.40, 2.08)	(0.70, 2.08)
	95% CI	(1.54, 1.59)	(1.53, 1.61)	(1.52, 1.58)	(1.52, 1.59)
6.0 CPD	n	360	172	360	172
	Mean (SD)	1.51 (0.31)	1.50 (0.31)	1.41 (0.37)	1.40 (0.37)
	(Min, Max)	(0.61, 2.29)	(0.61, 2.29)	(0.61, 2.29)	(0.61, 2.21)
	95% CI	(1.47, 1.54)	(1.46, 1.55)	(1.37, 1.45)	(1.35, 1.46)
12.0 CPD	n	360	172	360	172
	Mean (SD)	0.92 (0.39)	0.89 (0.40)	0.81 (0.40)	0.80 (0.41)
	(Min, Max)	(0.31, 2.00)	(0.31, 2.00)	(0.31, 2.00)	(0.31, 2.00)
	95%CI	(0.88, 0.96)	(0.83, 0.95)	(0.76, 0.85)	(0.74, 0.87)
		0.96)			

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3

3.5.7 Increased Spectacle Independence

The SILVER (*Spectacle Independence Lens Vision Evaluation and Repurchase*) questionnaire was an 11 item assessment intended to evaluate spectacle use, quality of vision, satisfaction with vision, and subject willingness to have the same lens model implanted again. The first 3 items addressed frequency of spectacle wear (overall, for seeing objects up close, and for seeing objects at distance). The response scale for these spectacle wear items was a 4 point categorical scale, ranging from “none of the time” to “all of the time”. Increased spectacle independence was assessed based upon the percentage of subjects responding *“None of the Time”* to Item 1 on the SILVER questionnaire*: “How often do you wear eyeglasses or contact lenses overall?”*. The degree of subject use of spectacles at pre-surgical baseline and by visit is summarized in Table 36.

At the pre-surgical baseline assessment, both the ReSTOR Toric IOL and the Control IOL groups reported a high degree of use of eyeglasses or contact lenses. At 12 months (Visit 5), 75.7% of the ReSTOR Toric

group and 69.4% of the ReSTOR group reported no use of spectacles or contact lenses ("none of the time").

It should be noted that the SILVER questionnaire also asked about spectacle use for up close and distance vision (SILVER Items 2 and 3, respectively). At 12 months, 94.6% of the ReSTOR Toric group and 92.8% of the Control group reported no use of spectacles or contact lenses for distance vision. Overall, the findings show that the ReSTOR Toric IOL demonstrated increased spectacle independence at a rate similar of the Control multifocal IOL. For near vision, 72.5% of the ReSTOR Toric group and 70.0% of the Control group reported no use of spectacles or contact lenses.

Table 36. Frequency (Overall*) of Wearing Spectacles or Contact Lenses by Visit (All Implanted Population)

		ReSTOR Toric IOL		Control IOL	
		N	%	N	%
Screening		385		188	
	None of the Time	8	2.1	9	4.8
	Some of the Time	61	15.8	32	17.0
	Most of the Time	90	23.4	56	29.8
	All of the Time	226	58.7	91	48.4
Visit 4		378		186	
	None of the Time	291	77.0	129	69.4
	Some of the Time	78	20.6	53	28.5
	Most of the Time	7	1.9	3	1.6
	All of the Time	2	0.5	1	0.5
Visit 5		371		180	
	None of the Time	281	75.7	125	69.4
	Some of the Time	79	21.3	53	20.4
	Most of the Time	6	1.6	1	0.6
	All of the Time	5	1.3	1	0.6

* Response to Item 1 on the SILVER questionnaire*: "How often do you wear eyeglasses or contact lenses overall"?*

3.5.8 Effectiveness Conclusions

The ReSTOR Toric IOL was non-inferior to the parent Control IOL in both UCDVA and UCNVA in the first eye at 12 months. The binocular defocus curve demonstrated the expected shift in near visual acuity peak from 33 cm to 40 cm and an improvement of approximately 2 lines of intermediate visual acuity for the ReSTOR Toric IOL compared to the parent Control IOL. No clinically relevant difference in the contrast sensitivity (photopic and mesopic, with and without a glare source) were observed between the ReSTOR Toric IOL and the Control IOL.

The ReSTOR Toric IOL provided increased spectacle independence based on SILVER Item 1, and was comparable to the Control IOL (75.7% - ReSTOR Toric IOL vs. 69.4% - Control IOL). The ReSTOR Toric IOL provides additional benefits to patients with pre-existing corneal astigmatism who require cataract

extraction and IOL implantation by providing these patients with near, intermediate, and distance vision, reduced residual refractive cylinder, and increased post-surgical spectacle independence.

3.6 SAFETY FINDINGS

Overall, as demonstrated by the data from Clinical Study C-09-036, no unanticipated safety concerns were identified with the ReSTOR Toric IOL. Further, the safety experience with the ReSTOR Toric IOL supports approval of the device and is similar to that observed with currently marketed monofocal, monofocal toric, and multifocal lenses by Alcon based on the safety information provided in the Package Inserts.

3.6.1 Actual and Potential SSIs Due to Optical Properties

The primary safety objective from our clinical study was the rate of actual and potential secondary surgical interventions (SSIs) related to the optical properties of the IOL. There were no pre-specified success criteria for this objective due to the lack of prior knowledge of the expected rate of SSIs due to optical properties. Therefore, clinical judgment was used to assess acceptable differences in SSIs due to optical properties between groups based on the effectiveness achieved.

The definition for SSIs due to optical properties was developed based upon discussions and feedback received from the FDA:

- IOL misalignment or rotation
- IOL tilt and decentration
- Visual disturbances and distortions
- Unanticipated refractive outcomes

The types of secondary surgical interventions the IOL included IOL repositioning and IOL replacement. The investigators were provided detail guidance in the protocol and at the investigator training in order to understand how to properly classify SSIs related to the optical properties of the IOL. Further, a proactive approach was developed in order to accurately define the rate of actual and potential SSIs related to the optical properties of the IOL, which is shown in Figure 16. The consideration for an SSI came from 3 sources:

- Investigator assessment of the subject,
- Spontaneous complaints of visual symptoms by subjects, and
- Proactive queries of the patients utilizing the APPLES questionnaire, which was an approach based upon discussion with the FDA.

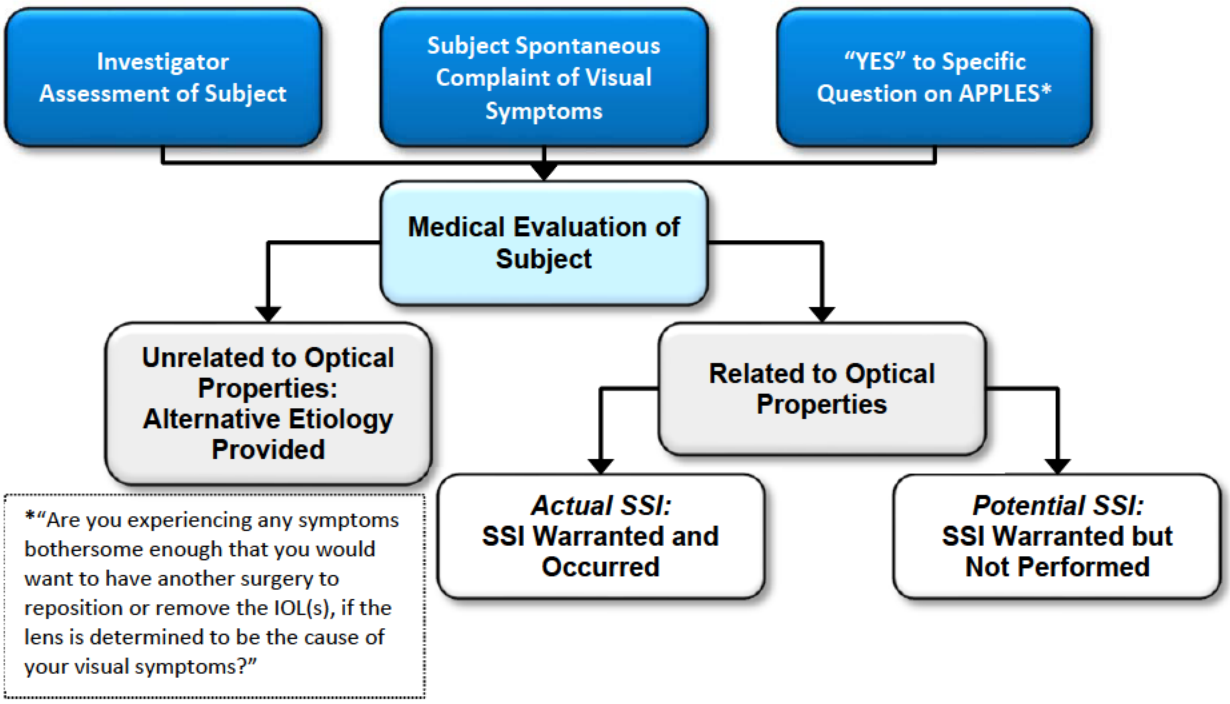
Each report then required a medical evaluation by the investigator of the subject to assess whether the event was related to the optical properties of the lens given the definition above.

If the SSI was related to optical properties, each event was then categorized in two categories:

- *actual SSI*, if an SSI was performed, or
- *potential SSI,* if an SSI was warranted but was not performed.

It is more important to determine the rate of subjects that may require an intervention due to optical properties rather than whether the subject actually underwent an intervention. Thus, both *actual* and *potential SSIs* due to optical properties were included in the primary safety endpoint with equal weighting.

Figure 16. Proactive Approach to the Collection of SSIs due to Optical Properties of the IOL



As shown in Table 37, the rate of actual or potential SSIs due to the optical properties for the ReSTOR Toric group was similar to subjects implanted with the Control group with the following numbers of SSIs due to optical properties:

- ReSTOR Toric group: no *actual* SSIs and 6 *potential* SSIs, and
- Control group: 4 *actual* SSIs and 4 *potential* SSIs.

Although no *actual* secondary surgical interventions due to optical properties were performed during the study for the ReSTOR Toric group, *potential* SSIs were reported and have equal weighting in the

primary safety endpoint. Two subjects in the control group underwent IOL replacement in both eyes due to severe visual disturbances that included glare, halos, and starbursts.

An overview of the SSIs due to optical properties reported with both groups is included in Appendix 2.

Table 37. Incidence and Confidence Limits of Actual and Potential SSIs Due to Optical Properties (Safety Population)

	ReSTOR Toric IOL				Control IOL				Difference	
	N	n	(%)	90% CI	N	n	(%)	90% CI	%	90% CI
First Implanted Eye	386	4	(1.04)	(0.00, 0.02)	188	4	(2.13)	(0.01, 0.05)	(-1.09)	(-0.08, 0.06)
Second Implanted Eye	383	2	(0.52)	(0.00, 0.02)	188	4	(2.13)	(0.01, 0.05)	(-1.61)	(-0.09, 0.06)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
CI = Confidence interval
SSI = Secondary Surgical Interventions

n Table 37, which is the primary analysis of safety, the 19 subjects who discontinued the study early were included in the analysis. All 19 subjects had attempted IOL implantation (successful or aborted contact with the eye) and thus met the criteria for inclusion in the primary safety analysis. To study the impact of these 19 subjects on the primary safety analysis, a sensitivity analysis was done whereby the 19 subjects were excluded from the analysis. The results of this sensitivity analysis are qualitatively similar to the analysis in Table 37 in that the bounds of the confidence interval are identical.

3.6.2 Rate of Severe Visual Disturbances/Distortions (Secondary Safety Objective)

The secondary safety objective was to estimate the rate of severe visual disturbances/distortions as reported by the subjects completing the APPLES questionnaire at 12 months (Visit 5).

Table 38 summarizes individual event rates and also provides the rate of any subject reporting a severe event at Month 12. Halos, starbursts and glare were the most frequently reported visual disturbances at 12 months. Reports of all other severe visual disturbances and distortions were reported by less than 2% of subjects in either group. Overall, the rate of severe visual disturbances/distortions at 12 months (Visit 5) was similar in subjects implanted with the ReSTOR Toric IOL (11.0%) relative to subjects implanted with the Control IOL (14.3%).

Table 38. Number and Percentage of Subjects with Severe Ratings on APPLES Questionnaire (Safety Population)

	ReSTOR Toric IOL			Control IOL		
Severe visual Disturbances/Distortions at 12 Months	**N**	**n**	**(%)**	**N**	**n**	**(%)**
Number of Subjects Reporting a Severe Event	**372**	**41**	**(11.0)**	**182**	**26**	**(14.3)**
Blurred vision	372	3	(0.8)	182	0	(0.0)
Color distortion	371	0	(0.0)	182	0	(0.0)
Distortion where flat lines look curved	372	0	(0.0)	182	0	(0.0)
Distortion where straight lines look tilted	372	0	(0.0)	182	0	(0.0)
Double vision	372	3	(0.8)	182	0	(0.0)
Feeling sick due to visual distortion	371	0	(0.0)	182	1	(0.5)
Glare	372	13	(3.5)	182	5	(2.7)
Halos	372	28	(7.5)	182	20	(11.0)
Hazy vision	372	5	(1.3)	182	1	(0.5)
Starbursts	372	16	(4.3)	182	16	(8.8)

For 14 ReSTOR Toric subjects and 6 Control subjects, the data was not available at 12 months. With the exception of 1 ReSTOR Toric subject that refused to complete the questionnaire at the 12 month visit, the other subjects did not complete the study as discussed in Table 11.

3.6.3 Adverse Events

3.6.3.1 Cumulative and Persistent Adverse Events

There are recognized safety and performance standards for clinical studies with IOLs as established by the International Standard Organization or ISO. Certain serious adverse events (e.g., ocular secondary surgical interventions) were predefined in the clinical study protocol and were evaluated against Safety and Performance Endpoints (SPE) defined in EN ISO 11979-7: 2006. It is important to note that these ISO standards were developed based on monofocal IOLs rather than multifocal IOLs.

Secondary surgical interventions included any ocular surgical procedure performed after the start of cataract surgery. Examples included but were not limited to the following:

- IOL repositioning
- IOL replacement
- Vitrectomy
- Wound leak repair
- Intravitreal injections
- YAG laser to treat pathologies other than PCO

The actual rates of certain serious adverse events from our study were compared to the SPE rates in Table 39. Except for SSIs, the observed cumulative adverse event rates were not statistically significantly greater than SPE rate in the ISO guidance. At 12 months, a persistent serious adverse event for cystoid

macular oedema was observed in the first and second eye of one subject who had been implanted with the ReSTOR Toric IOL.

Since SSIs exceeded the SPE rate for the first and second eyes of the ReSTOR Toric IOL group as well as the second eyes of the Control IOL group, it is important to review all secondary surgical interventions to fully understand the safety profile of the ReSTOR Toric IOL. All secondary surgical interventions that occurred during Clinical Study C-09-036, regardless of investigator causality, are presented in Table 40. The SSIs were placed into general categories based on the characteristics of the event provided by the site:

- As previously discussed in Section 3.6.1., no SSIs *related to the optical properties of the IOL* were reported in the ReSTOR Toric IOL group per the investigator; however, IOL replacements due to visual disturbances occurred in 2 subjects in both eyes in the control group.
- In the ReSTOR Toric IOL group, a SSI was related but *not due to the optical properties of the lens***.** For this case, the investigator had to reposition the lens because the haptic was outside of the capsular bag.
- For 5 eyes (3 first eyes, 2 second eyes), the investigator did not attribute the SSI to the ReSTOR Toric IOL; however, a Sponsor assessment concluded that the *relationship to the IOL could not be ruled out*.
- The *surgeon error* category includes IOL repositionings attributed to surgeon error at the time of implantation. Prior to closing the wound, the surgeon was to determine the alignment of the toric axis with the reference marks on the eye. As confirmed by PALO measurements on the day of surgery, the IOL was not placed at the intended axis as the surgeon was unable to place the IOL accurately because of a subject factor (e.g., floppy iris syndrome).
- The *attributed to surgery* category include events that are typically associated with cataract surgery and could occur with the implantation of any IOL.
- Those events in the *refractive correction* category include limbal relaxing incisions since the ReSTOR IOL did not correct for astigmatism. These events occurred after study exit.
- In the *therapeutic procedure* category, the events include SSIs to treat a subject's condition during study. Cataract surgery is a documented risk for the development of retinal conditions (Feltgen 2013, Patterson 2001).

Thus, in summary, although the overall SSI rate for the ReSTOR Toric IOL (first and second eyes) exceeded the SPE grid rate provided in the ISO guidance, a majority of the events were not related to the IOL according to the investigator or a Sponsor assessment. Further, the second eyes of the Control IOL also exceeded the SPE grid rate.

Table 39. Cumulative and Persistent Adverse Events (Safety Population)

	First Implanted Eye						Second Implanted Eye					
	ReSTOR Toric IOL (N=386)			Control IOL (N=188)			ReSTOR Toric IOL (N=383)			Control IOL (N=188)		
	n	%	SPE %	p-value[a]	n	%	SPE %	p-value[a]	n	%	SPE %	p-value[a]	n	%	SPE %	p-value[a]
Cumulative Events																
Corneal oedema	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000
Cystoid macular oedema	1	(0.3)	3.0	1.000	0	(0.0)	3.0	1.000	3	(0.8)	3.0	0.997	1	(0.5)	3.0	0.978
Endophthalmitis	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000
Hypopyon	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000
Iritis	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000
Lens dislocated from posterior chamber	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000
Pupillary block	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000	0	(0.0)	0.1	1.000
Retinal detachment	1	(0.3)	0.3	0.322	0	(0.0)	0.3	1.000	2	(0.5)	0.3	0.319	1	(0.5)	0.3	0.432
Secondary surgical intervention	12	(3.1)	0.8	0.000	4	(2.1)	0.8	0.065	11	(2.9)	0.8	0.000	6	(3.2)	0.8	0.004
Raised IOP requiring treatment	0	(0.0)	0.4	1.000	0	(0.0)	0.4	1.000	0	(0.0)	0.4	1.000	0	(0.0)	0.4	1.000
Persistent Events																
Corneal oedema	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000
Cystoid macular oedema	1	(0.3)	0.5	0.575	0	(0.0)	0.5	1.000	1	(0.3)	0.5	0.571	0	(0.0)	0.5	1.000
Iritis	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000	0	(0.0)	0.3	1.000
Raised IOP requiring treatment	0	(0.0)	0.4	1.000	0	(0.0)	0.4	1.000	0	(0.0)	0.4	1.000	0	(0.0)	0.4	1.000

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
SPE = Safety and Performance Endpoints (EN ISO 11979-7:2006)
[a] One-sided exact binomial test (alpha = .05)
Persistent Serious Adverse Events are a subset of Cumulative Serious Adverse Events.

Table 40. All Secondary Surgical Interventions (Safety Population)

	First Implanted Eye		Second Implanted Eye	
	ReSTOR Toric IOL (N=386)	Control IOL (N=188)	ReSTOR Toric IOL (N=383)	Control IOL (N=188)
All Secondary Surgical Interventions	**12 (3.1)**	**4 (2.1)**	**11 (2.9)**	**6 (3.2)**
Related to Optical Properties	**-**	**2 (1.1)**	**-**	**2 (1.1)**
IOL replacement due to visual disturbances	0	2	0	2
Related to Non-Optical Properties	**1 (0.3)**	**-**	**-**	**-**
IOL repositioning due to haptic outside of bag	1	0	0	0
Relationship to IOL Cannot be Ruled Out	**3 (0.8)**	**-**	**2 (0.5)**	**-**
IOL repositioning due to IOL misalignment	1[a]	0	0	0
Astigmatic keratotomy and/or LASIK to correct residual refractive error	1	0	1	0
Limbal relaxing incision to correct surgically induced astigmatism	1	0	1	0
Surgeon Error	**3 (0.8)**	**-**	**-**	**-**
IOL repositioning due to inaccurate IOL placement	3[b,c]	0	0	0
Attributed to Surgery	**4 (1.0)**	**-**	**5 (1.3)**	**2 (1.1)**
Anterior vitrectomy	1	0	0	0
Corneal wound leak repair	0	0	1	1
Retained lens removal	2	0	1	1
YAG laser capsulotomy for wrinkles, folds or strands in capsule	1[b]	0	3	0
Refractive Correction	**-**	**1 (0.5)**	**-**	**1 (0.5)**
Limbal relaxing incision to correct pre-existing astigmatism	0	1	0	1
Therapeutic Procedures	**2 (0.5)**	**1 (0.5)**	**4 (1.0)**	**1 (0.5)**
Macular hole repair	0	0	1	0
Intraocular injection for wet age related macular degeneration	0	1[d]	0	0
Retinal detachment repair and prophylactic retinopexy[e]	2	0	3	1

[a] One subject required an IOL repositioning surgery at Month 6. The Investigator considered the SSI related to the patient's eye anatomy and the IOL rotation was assumed to have occurred within 24 hours following surgery.
[b] One subject experienced floppy iris during surgery and required 2 repositioning procedures. The subject also experienced a YAG laser capsulotomy for wrinkled capsule.
[c] The IOL was implanted at the incorrect axis for 2 eyes.
[d] One subject had two intraocular injections.
[e] One subject had 1 prophylactic retinopexy procedure performed in the first eye and 3 retinopexy procedures performed in the second eye.

3.6.3.2 Adverse Device Effects

Ocular adverse device effects (ADEs) are any adverse events assessed as related to the device per the investigator assessment and are presented in Table 41. As some descriptors are general in nature, further clarity is provided below for certain ADEs in Table 41:

- In the ReSTOR Toric IOL group, the event of *IOL repositioning* was due to the distal haptic being outside of the capsular bag. The distal haptic outside of the capsular bag was captured as an adverse event of *device dislocation.*
- The *IOL replacement* for the Control IOL group was due to optical properties and was discussed in Section 3.6.1.
- The events coded as *visual impairment* includes subject complaints of unclear near vision for the ReSTOR Toric IOL group and words running together while reading or watching TV for the Control IOL group.

The rate of eyes experiencing any ocular ADEs in the ReSTOR Toric IOL group was 0.8% in both the first and second eye, compared to 1.6% and 2.7% in the Control IOL group. There were no UADEs during the study. There were no non-ocular ADEs during the study. Further, no ADE was reported in more than 2 eyes in the ReSTOR Toric group.

Table 41. Ocular Adverse Device Effects (Safety Population)

	First Implanted Eye						Second Implanted Eye					
	ReSTOR Toric IOL (N=386)			Control IOL (N=188)			ReSTOR Toric IOL (N=383)			Control IOL (N=188)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Any eye with an ADE	**3**	**(0.8)**	**6**	**3**	**(1.6)**	**4**	**3**	**(0.8)**	**5**	**5**	**(2.7)**	**6**
Device dislocation	1	(0.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Capsulorhexis tear	0	(0.0)	0	0	(0.0)	0	1	(0.3)	1	0	(0.0)	0
Glare	1	(0.3)	1	0	(0.0)	0	1	(0.3)	1	0	(0.0)	0
Halo vision	1	(0.3)	1	1	(0.5)	1	1	(0.3)	1	2	(1.1)	2
Photopsia	1	(0.3)	1	0	(0.0)	0	1	(0.3)	1	0	(0.0)	0
IOL Repositioning of Haptic	1	(0.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
IOL Replacement	0	(0.0)	0	2	(1.1)	2	0	(0.0)	0	2	(1.1)	2
Vision blurred	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.5)	1
Visual impairment	1	(0.3)	1	1	(0.5)	1	1	(0.3)	1	1	(0.5)	1

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
If an eye has multiple occurrences of an AE, the eye was presented only once in the respective eye count (n).
Events are counted each time in the event (E) column. Events recorded as OU (both eyes) were counted once for the first eye and sec ond eye.

3.6.3.3 All Ocular Adverse Events

The incidence of ocular AEs are presented for the first eye in Table 42 and for the second eye in Table 43. The types of all ocular AEs reported were similar between the ReSTOR Toric IOL and Control IOL groups.

In 3 categories of ocular AEs, the ReSTOR Toric IOL group was numerically higher than the Control IOL group for both the first (Table 42) and second eyes (Table 43):

- None of the events in the *iris disorders category* were related to the IOL. In general, the events were reported within 2 months postoperative, and all but three events (iris atrophy, n=2 and iris transillumination defect, n=1) resolved during the conduct of the study.
- All of the events in the *ocular hypertension category* were reported within 1 week postoperative and subsequently resolved with treatment.
- The *other eye disorders* include a variety of general eye conditions that did not fit into the more specific categories. Only one of these events (eye injury described as a capsulorhexis tear due to IOL haptic break, which is described in Section 3.6.4.2.) was related to the ReSTOR Toric IOL. Further, all of these events were mild or moderate in intensity.

Thus, the pattern of ocular AEs observed were generally consistent with those expected in the target population or those subjects undergoing cataract surgery.

Table 42. Ocular Adverse Events for First Implanted Eye (Safety Population)

	ReSTOR Toric IOL (N=386)				Control IOL (N=188)			
	n	(%)	UCL	E	n	(%)	UCL	E
Capsular Disorders	**35**	**(9.1)**	**11.8**	**35**	**17**	**(9.0)**	**13.3**	**17**
Posterior capsule opacification	35	(9.1)	11.8	35	17	(9.0)	13.3	17
Ciliary Body Disorders	**1**	**(0.3)**	**1.2**	**1**	**0**	**(0.0)**	**1.6**	**0**
Ciliary zonular dehiscence	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Conjunctival Disorders	**5**	**(1.3)**	**2.7**	**5**	**4**	**(2.1)**	**4.8**	**5**
Conjunctival haemorrhage	1	(0.3)	1.2	1	2	(1.1)	3.3	2
Conjunctival hyperaemia	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Conjunctivitis	2	(0.5)	1.6	2	2	(1.1)	3.3	2
Conjunctivitis allergic	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Pinguecula	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Corneal Disorders	**12**	**(3.1)**	**5.0**	**13**	**6**	**(3.2)**	**6.2**	**7**
Corneal abrasion	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Corneal dystrophy	3	(0.8)	2.0	3	0	(0.0)	1.6	0
Corneal oedema	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Corneal opacity	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Corneal striae	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Punctate keratitis	4	(1.0)	2.4	4	5	(2.7)	5.5	5
Eyelid Disorders	**7**	**(1.8)**	**3.4**	**7**	**7**	**(3.7)**	**6.9**	**8**
Benign neoplasm of eyelid	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Blepharitis	2	(0.5)	1.6	2	4	(2.1)	4.8	4
Cutis laxa	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Eyelid margin crusting	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Meibomianitis	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Myokymia	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Trichiasis	1	(0.3)	1.2	1	0	(0.0)	1.6	0
VIIth nerve paralysis	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Iris Disorder	**6**	**(1.6)**	**3.0**	**6**	**1**	**(0.5)**	**2.5**	**1**
Iris adhesions	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Iris atrophy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Iritis	4	(1.0)	2.4	4	1	(0.5)	2.5	1
Lacrimal Disorders	**21**	**(5.4)**	**7.7**	**23**	**13**	**(6.9)**	**10.8**	**13**
Dry eye	9	(2.3)	4.0	10	9	(4.8)	8.2	9
Eye discharge	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Keratoconjunctivitis sicca	9	(2.3)	4.0	9	3	(1.6)	4.1	3
Lacrimation decreased	3	(0.8)	2.0	3	0	(0.0)	1.6	0
Lacrimation increased	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Ocular Hypertension	**4**	**(1.0)**	**2.4**	**4**	**0**	**(0.0)**	**1.6**	**0**
Intraocular pressure increased	4	(1.0)	2.4	4	0	(0.0)	1.6	0

	ReSTOR Toric IOL (N=386)				Control IOL (N=188)			
	n	(%)	UCL	E	n	(%)	UCL	E
Other Cataract Procedure Complications	**3**	**(0.8)**	**2.0**	**3**	**0**	**(0.0)**	**1.6**	**0**
Cataract operation complication	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Device dislocation	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Other Disorders	**17**	**(4.4)**	**6.5**	**20**	**4**	**(2.1)**	**4.8**	**4**
Binocular eye movement disorder	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Drug hypersensitivity	1	(0.3)	1.2	2	0	(0.0)	1.6	0
Eye allergy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Eye disorder	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Eye injury	3	(0.8)	2.0	3	0	(0.0)	1.6	0
Eye irritation	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Eye naevus	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Eye pain	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Eye pruritus	3	(0.8)	2.0	3	0	(0.0)	1.6	0
Foreign body sensation in eyes	0	(0.0)	0.8	0	2	(1.1)	3.3	2
Heterophoria	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Muscle twitching	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Ocular hyperaemia	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinal Disorders	**6**	**(1.6)**	**3.0**	**7**	**4**	**(2.1)**	**4.8**	**4**
Age-related macular degeneration	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Cystoid macular oedema	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Diabetic retinopathy	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Macular reflex abnormal	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Maculopathy	2	(0.5)	1.6	3	0	(0.0)	1.6	0
Retinal degeneration	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinal detachment	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinal pigment epitheliopathy	0	(0.0)	0.8	0	2	(1.1)	3.3	2
Surgical and Medical Procedures	**13**	**(3.4)**	**5.3**	**16**	**4**	**(2.1)**	**4.8**	**5**
Corneal operation	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Curetting of chalazion	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Eye laser surgery	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Intra-ocular injection	0	(0.0)	0.8	0	1	(0.5)	2.5	2
Intraocular lens repositioning	4	(1.0)	2.4	5	0	(0.0)	1.6	0
Keratomileusis	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Keratotomy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinopexy	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Surgical procedure repeated	3	(0.8)	2.0	3	2	(1.1)	3.3	2
Vitrectomy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Vitreous Disorders	**15**	**(3.9)**	**5.9**	**15**	**8**	**(4.3)**	**7.5**	**8**
Vitreous detachment	7	(1.8)	3.4	7	7	(3.7)	6.9	7

	ReSTOR Toric IOL (N=386)				Control IOL (N=188)			
	n	**(%)**	**UCL**	**E**	**n**	**(%)**	**UCL**	**E**
Vitreous floaters	6	(1.6)	3.0	6	1	(0.5)	2.5	1
Vitreous opacities	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Vitreous prolapse	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Visual Impairment	**11**	**(2.8)**	**4.7**	**16**	**6**	**(3.2)**	**6.2**	**8**
Diplopia	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Glare	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Halo vision	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Photophobia	1	(0.3)	1.2	1	2	(1.1)	3.3	2
Photopsia	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Refraction disorder	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Vision blurred	4	(1.0)	2.4	4	1	(0.5)	2.5	1
Visual acuity reduced	1	(0.3)	1.2	2	0	(0.0)	1.6	0
Visual impairment	1	(0.3)	1.2	1	2	(1.1)	3.3	2

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Adverse Events coded using MedDRA
UCL - 95% one-sided upper confidence limit using Clopper-Pearson exact test
If an eye has multiple occurrences of an AE, the eye was presented only once in the respective eye count (n).
Events are counted each time in the event (E) column. Events recorded as OU (both eyes) were counted once for the first eye an d second eye.

Table 43. Ocular Adverse Events for Second Implanted Eye (Safety Population)

	ReSTOR Toric IOL (N=383)				Control IOL (N=188)			
	n	(%)	UCL	E	n	(%)	UCL	E
Capsular Disorders	**33**	**(8.6)**	**11.4**	**33**	**19**	**(10.1)**	**14.5**	**19**
Anterior capsule contraction	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Posterior capsule opacification	32	(8.4)	11.1	32	19	(10.1)	14.5	19
Conjunctival Disorders	**9**	**(2.3)**	**4.1**	**9**	**5**	**(2.7)**	**5.5**	**5**
Conjunctival haemorrhage	5	(1.3)	2.7	5	2	(1.1)	3.3	2
Conjunctival hyperaemia	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Conjunctivitis	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Conjunctivitis allergic	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Dermal cyst	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Corneal Disorders	**10**	**(2.6)**	**4.4**	**13**	**4**	**(2.1)**	**4.8**	**5**
Corneal defect	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Corneal degeneration	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Corneal disorder	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Corneal dystrophy	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Corneal oedema	3	(0.8)	2.0	3	1	(0.5)	2.5	1
Corneal opacity	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Corneal striae	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Keratitis	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Punctate keratitis	3	(0.8)	2.0	3	3	(1.6)	4.1	3
Eyelid Disorders	**5**	**(1.3)**	**2.7**	**6**	**7**	**(3.7)**	**6.9**	**7**
Benign neoplasm of eyelid	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Blepharitis	0	(0.0)	0.8	0	4	(2.1)	4.8	4
Chalazion	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Cutis laxa	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Dermatitis allergic	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Eyelid margin crusting	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Meibomianitis	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Iris Disorder	**6**	**(1.6)**	**3.1**	**6**	**2**	**(1.1)**	**3.3**	**2**
Floppy iris syndrome	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Iris atrophy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Iris transillumination defect	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Iritis	3	(0.8)	2.0	3	2	(1.1)	3.3	2
Lacrimal Disorders	**20**	**(5.2)**	**7.5**	**21**	**14**	**(7.4)**	**11.4**	**14**
Dry eye	8	(2.1)	3.7	8	10	(5.3)	8.9	10
Keratoconjunctivitis sicca	11	(2.9)	4.7	11	4	(2.1)	4.8	4
Lacrimation decreased	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Lacrimation increased	1	(0.3)	1.2	1	0	(0.0)	1.6	0

	ReSTOR Toric IOL (N=383)				Control IOL (N=188)			
	n	(%)	UCL	E	n	(%)	UCL	E
Ocular Hypertension	**4**	**(1.0)**	**2.4**	**4**	**1**	**(0.5)**	**2.5**	**1**
Intraocular pressure increased	4	(1.0)	2.4	4	1	(0.5)	2.5	1
Other Cataract Procedure Complications	**2**	**(0.5)**	**1.6**	**2**	**2**	**(1.1)**	**3.3**	**2**
Cataract operation complication	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Wound complication	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Other Disorders	**22**	**(5.7)**	**8.1**	**26**	**8**	**(4.3)**	**7.5**	**10**
Binocular eye movement disorder	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Drug hypersensitivity	1	(0.3)	1.2	3	0	(0.0)	1.6	0
Eye allergy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Eye disorder	4	(1.0)	2.4	4	0	(0.0)	1.6	0
Eye inflammation	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Eye injury	5	(1.3)	2.7	5	0	(0.0)	1.6	0
Eye irritation	1	(0.3)	1.2	1	2	(1.1)	3.3	2
Eye pain	2	(0.5)	1.6	2	2	(1.1)	3.3	2
Eye pruritus	3	(0.8)	2.0	3	1	(0.5)	2.5	1
Foreign body sensation in eyes	2	(0.5)	1.6	2	3	(1.6)	4.1	3
Heterophoria	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Muscle twitching	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Ocular discomfort	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Ocular hyperaemia	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Retinal Disorders	**12**	**(3.1)**	**5.0**	**18**	**8**	**(4.3)**	**7.5**	**10**
Age-related macular degeneration	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Cystoid macular oedema	3	(0.8)	2.0	3	1	(0.5)	2.5	1
Diabetic retinopathy	0	(0.0)	0.8	0	2	(1.1)	3.3	2
Macular degeneration	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Macular hole	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Macular oedema	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Maculopathy	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Optic atrophy	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinal aneurysm	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Retinal degeneration	3	(0.8)	2.0	3	0	(0.0)	1.6	0
Retinal detachment	2	(0.5)	1.6	3	1	(0.5)	2.5	1
Retinal exudates	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Retinal haemorrhage	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinal pigment epitheliopathy	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Retinal tear	2	(0.5)	1.6	3	0	(0.0)	1.6	0
Surgical and Medical Procedures	**11**	**(2.9)**	**4.7**	**13**	**6**	**(3.2)**	**6.2**	**7**
Corneal operation	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Eye laser surgery	3	(0.8)	2.0	3	0	(0.0)	1.6	0
Keratomileusis	1	(0.3)	1.2	1	0	(0.0)	1.6	0

	ReSTOR Toric IOL (N=383)				Control IOL (N=188)			
	n	**(%)**	**UCL**	**E**	**n**	**(%)**	**UCL**	**E**
Retinal operation	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Retinopexy	3	(0.8)	2.0	5	1	(0.5)	2.5	1
Skin lesion excision	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Surgical procedure repeated	1	(0.3)	1.2	1	3	(1.6)	4.1	3
Suture insertion	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Vitreous Disorders	**16**	**(4.2)**	**6.3**	**16**	**6**	**(3.2)**	**6.2**	**6**
Vitreous detachment	10	(2.6)	4.4	10	4	(2.1)	4.8	4
Vitreous floaters	5	(1.3)	2.7	5	1	(0.5)	2.5	1
Vitreous opacities	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Vitreous prolapse	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Visual Impairment	**12**	**(3.1)**	**5.0**	**16**	**8**	**(4.3)**	**7.5**	**9**
Diplopia	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Glare	2	(0.5)	1.6	2	1	(0.5)	2.5	1
Halo vision	2	(0.5)	1.6	2	2	(1.1)	3.3	2
Migraine with aura	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Photophobia	1	(0.3)	1.2	1	1	(0.5)	2.5	1
Photopsia	2	(0.5)	1.6	2	0	(0.0)	1.6	0
Refraction disorder	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Scotoma	0	(0.0)	0.8	0	1	(0.5)	2.5	1
Vision blurred	4	(1.0)	2.4	4	2	(1.1)	3.3	2
Visual acuity reduced	1	(0.3)	1.2	1	0	(0.0)	1.6	0
Visual impairment	1	(0.3)	1.2	1	1	(0.5)	2.5	1

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Adverse Events coded using MedDRA
UCL - 95% one-sided upper confidence limit using Clopper-Pearson exact test
If an eye has multiple occurrences of an AE, the eye was presented only once in the respective eye count (n).
Events are counted each time in the event (E) column. Events recorded as OU (both eyes) were counted once for the first eye an d second eye.

3.6.3.4 Adverse Events Leading to Study Discontinuation

Of the 5 subjects that discontinued from the study due to an adverse event, 4 were implanted with the ReSTOR Toric IOL and 1 was implanted with the Control IOL. None of the events were related to the surgical procedure or the IOL, and all of them were non-ocular adverse events.

ReSTOR Toric

Subject C09036 (b)(6) was implanted with IOL Model SND1T4 in the right eye (OD) and IOL Model SND1T3 in the left eye (OS). The subject died (cause of *death unknown*) prior to study completion. The event was not related to the device or surgical procedure.

Subject C09036 (b)(6) was implanted with IOL Model SND1T4 in the right eye (OD) and IOL Model SND1T3 in the left eye (OS). The subject experienced *acute renal failure* that was fatal and died prior to study completion. The event was not related to the device or surgical procedure.

Subject C09036 (was implanted with IOL Model SND1T3 in the left eye (OS) and IOL Model SND1T3 in the right eye (OD). The subject experienced a non-fatal *cerebrovascular accident* and exited from the study. The event was not related to the device or surgical procedure.

Subject C09036 (b)(6) was implanted with IOL Model SND1T4 in the right eye (OD) and IOL Model SND1T3 in the left eye (OS). The subject experienced *acute renal failure* that was fatal and died prior to study completion. The event was not related to the device or surgical procedure.

Control

Subject C09036 (b)(6) was implanted with IOL Model SA60D3 in the left eye (OS) and IOL Model SA60D3 in the right eye (OD). The subject experienced a *cardiac arrest* that was fatal and died prior to study completion. The event was not related to the device or surgical procedure.

3.6.4 Other Safety Findings

In addition to the collection of adverse events, other supportive safety data were collected during the study and will be discussed in this section.

3.6.4.1 Device Deficiencies

A device deficiency was defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. The investigators examined the ReSTOR Toric or control IOLs before and immediately after implantation on the surgery day as requested by the clinical study protocol.

The following details can be noted about these 4 cases with additional information provided in Table 44:

- Three device deficiencies were reported due to damage of the IOL haptics while handling the IOL either prior to, during or after the surgical procedure. Of these 3 device deficiencies, one had subject impact, which is discussed further in Section 3.6.4.2. Both the ReSTOR Toric and Control IOLs are manually loaded into the cartridge as shown in Figure 17.
- In the control group, 1 device deficiency was reported for a damaged IOL box.

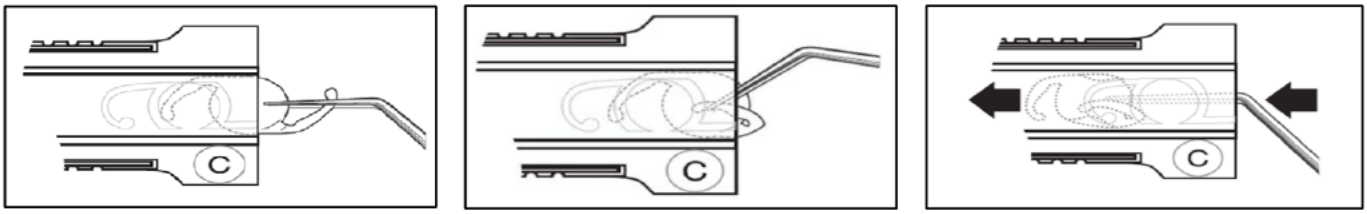
Thus, overall device deficiencies were infrequent during the study. Four device deficiencies were reported during the conduct of Clinical Study C-09-036, and 1 device deficiency had subject impact.

Table 44. Overview of Device Deficiencies from Clinical Study C-09-036

Subject	Group	Subject Impact	Device Deficiency Description
(b) (6)	ReSTOR Toric	Yes	• *IOL haptic broke*, which was noted following implantation, resulting in capsular tear • IOL explanted and subject successfully implanted with non-study IOL
	ReSTOR Toric	No	• *IOL haptic broke* when caught in cartridge. • IOL did not touch eye • Eye successfully implanted with back-up ReSTOR Toric IOL
	Control	No	• IOL developed *kinked haptic* when loaded by technician • IOL did not touch eye • Eye successfully implanted with back-up ReSTOR Toric IOL
	Control	No	• *Damaged box* upon receipt; Wrapper intact

*Not associated with a particular subject.

Figure 17. Manual Loading of ReSTOR Toric and Control IOLs into Cartridge



3.6.4.2 Surgical Problems

Surgical problems occurred infrequently in both IOL groups (Table 44). Detailed narratives for each subject who experienced a capsulorhexis tear and/or an anterior capsular tear or zonular damage are provided in Appendix 3.

Capsulorhexis tear and Anterior radial tear

At the operative visit, capsulorhexis tear and/or anterior radial tear was experienced in 8 eyes in the ReSTOR Toric IOL group. A slightly higher incidence of capsulorhexis and anterior radial tears was noted in the ReSTOR Toric group. This is anticipated since there is a slight increased risk of a tear due to the extra manipulation needed to implant and orient a toric IOL. However, this is a manageable risk, especially for anterior tears that do not extend to the posterior portion of the capsular bag.

- In 7 eyes, the events were assessed by the Investigator as related to the surgical procedure (cataract surgery) and not the IOL being implanted.
- In 1 eye, the event was due to a broken IOL haptic following implantation of the ReSTOR Toric IOL. The ReSTOR Toric IOL required explantation; however, the subject was successfully implanted with a non-study IOL despite the capsulorhexis tear. The investigator did not provide explanation of cause of the breaking of the IOL.

Overall, 768 eyes were successfully implanted with the ReSTOR Toric IOL during Clinical Study C-09-036. One event of capsulorhexis tear was attributed to the ReSTOR Toric IOL itself. Further, those eyes in the ReSTOR Toric group that experienced capsulorhexis tear and/or anterior radial tear did not experience IOL tilt or decentration during the study and had a BCDVA of 0.16 logMAR or better at 12 months as provided in Appendix 3.

Thus, the capsulorhexis tears and anterior radial tears occurred infrequently in both groups with good postoperative visual outcomes for these subjects.

Zonular damage

Two subjects experienced zonular damage, 1 from each arm of the study. In both cases, the subjects had underlying conditions that contributed to the zonular damage. Thus, the investigators did not attribute the zonular damage to the IOL.

- One subject in the ReSTOR Toric group had diagnosis of pseudoexfoliation (PXF) syndrome at the pre-operative visit. Some studies that have found an increased rate of complications in eyes with PXF compared to eyes without PXF. Therefore, it is probable that the PXF may have contributed to the zonular dehiscence that occurred during cataract surgery (Akinci 2008, Drolsum 1998).
- One subject in the Control group had missing nasal zonules that necessitated the use of a capsular tension ring.

Table 41. Number and Percentage of Eyes with Capsulorhexis Tear and Anterior Radial Tear Or Zonular Damage (Safety Population)

	First Implanted Eye				Second Implanted Eye			
	ReSTOR Toric IOL (N = 386)		Control IOL (N = 188)		ReSTOR Toric IOL (N = 383)		Control IOL (N = 188)	
	n	(%)	n	(%)	n	(%)	n	(%)
Capsulorhexis tear & Anterior radial tear	3	(0.8)	1	(0.5)	5	(1.3)	0	(0.0)
Zonular damage	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.5)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3

3.6.4.3 Posterior Capsular Opacification (PCO)

A slit lamp examination was performed at all postoperative visits. The grading of PCO was predefined in the clinical protocol and assessed in 3 subjective categories, which were defined as follows:

- *Clinically non-significant* – Early development of PCO, including fibrosis and proliferation of lens epithelial cells, observable by slit lamp biomicroscopy. Causes no apparent decrease in visual acuity subjectively (e.g., glare) or objectively (e.g., decrease in visual acuity).
- *Clinically significant* – Increased PCO with early subjective and objective visual acuity changes but does not require secondary capsulotomy.
- *Clinically significant requiring YAG* – Clinically significant PCO adversely affecting subject's visual acuity and requiring posterior capsulotomy.

Table 45 shows worst-case subjective PCO at any post-operative visit, and Table 46 shows the number and percentage of eyes with posterior capsulotomy at any visit. Based on these data, no greater incidence of PCO and the need for YAG laser posterior capsulotomy was observed in the ReSTOR Toric group when compared to the Control group as demonstrated by these data points:

- The incidence of "clinically significant PCO requiring a YAG" was similar in the ReSTOR Toric group compared to the Control group, first eye: 9.6% vs. 9.6%; second eye: 8.9% vs. 10.1% (Table 45).
- The incidence of eyes undergoing YAG laser posterior capsulotomy at any visit was similar in the ReSTOR Toric group when compared to the Control group, first eye: 10.9% vs. 11.2%; second eye: 10.2% vs. 11.2% (Table 46).

In some instances, investigators performed YAG laser posterior capsulotomy for PCO even though the grading of PCO was not "clinically significant requiring YAG," so the number of subjects "requiring a YAG" and the number of subjects with posterior capsulotomy are not identical.

Although a slightly higher number of eyes in the ReSTOR Toric group experienced PCO of any grading compared to the control group [first eye: 59.8% vs. 56.4%; second eye: 59.3% vs. 55.3% (Table 43)], it has been shown that the AcrySof material has an adhesive surface that may contribute to reduced rates of PCO (Schmidbauer 2002, Apple 2001). Further, the square edges of the AcrySof IOL as depicted in Figure 6 through Figure 8 also reduce PCO rates in clinical practice (Wolken 2001).

Despite adding a toric correction to the posterior surface of the ReSTOR Toric IOL, there was not a large difference in the incidence of PCO or YAG capsulotomy between the two groups. However, even if PCO development occurs, a simple yet effective treatment of Nd: YAG laser posterior capsulotomy provides resolution for the subject.

Table 45. Worst Case Subjective Posterior Capsule Opacification at Any Post-Operative Visit (Safety Set)

	First Implanted Eye				Second Implanted Eye			
	ReSTOR Toric IOL (N = 386)		Control IOL (N = 188)		ReSTOR Toric IOL (N = 383)		Control IOL (N = 188)	
	n	(%)	n	(%)	n	(%)	n	(%)
None	155	(40.2)	82	(43.6)	156	(40.7)	84	(44.7)
Clinically non-significant	179	(46.4)	84	(44.7)	180	(47.0)	81	(43.1)
Clinically significant	15	(3.9)	4	(2.1)	13	(3.4)	4	(2.1)
Clinically significant requiring a YAG	37	(9.6)	18	(9.6)	34	(8.9)	19	(10.1)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3
Worst Case was defined as the highest grading of PCO observed for an eye at any time during follow-up.

Table 46. Number and Percentage of Eyes with Posterior Capsulotomy at Any Visit (Safety Set)

	First Implanted Eye				Second Implanted Eye			
	ReSTOR Toric IOL (N = 386)		Control IOL (N = 188)		ReSTOR Toric IOL (N = 383)		Control IOL (N = 188)	
	n	(%)	n	(%)	n	(%)	n	(%)
Yes	42	(10.9)	21	(11.2)	39	(10.2)	21	(11.2)
No	344	(89.1)	167	(88.8)	344	(89.8)	167	(88.8)

ReSTOR Toric IOL = ACRYSOF IQ ReSTOR Multifocal Lens Models SND1T3/SND1T4/SND1T5/SND1T6
Control IOL = ACRYSOF ReSTOR Multifocal Lens Model SA60D3

3.6.5 Safety Conclusions

Overall, as demonstrated by the data from Clinical Study C-09-036, no unanticipated safety concerns were identified with the ReSTOR Toric IOL. Based on safety parameters collected in this clinical trial, the safety profiles observed for the ReSTOR Toric IOL and the Control IOL were similar.

- Overall, as demonstrated by the data from Clinical Study C-09-036, no unanticipated safety concerns were identified with the ReSTOR Toric IOL.
- Overall, the rate of severe visual disturbances/distortions at 12 months (Visit 5) was similar in subjects implanted with the ReSTOR Toric IOL relative to subjects implanted with the Control IOL.
- Although the overall SSI rate for ReSTOR Toric (first and second eyes) exceeded the SPE grid rate provided in the ISO guidance, a majority of the events were not related to the IOL according to the investigator or a Sponsor assessment. The SSI rate for the second eyes of the Control IOL also exceeded the SPE grid rate.
- The rate of eyes experiencing any ocular ADEs was less than 1% in the ReSTOR Toric group.
- The types of all ocular AEs reported were similar between the ReSTOR Toric and Control groups.
- Of the 5 subjects that discontinued from the study for due to an adverse event, none of these non-ocular events were related to the surgical procedure or the IOL.
- Device deficiencies were infrequent during the study.
- The capsulorhexis tears and anterior radial tears occurred infrequently in both groups with good postoperative visual outcomes for these subjects.
- No greater incidence of PCO or the need for YAG laser posterior capsulotomy was observed in the ReSTOR Toric group when compared to the Control group.

4 GLOBAL EXPERIENCE WITH THE RESTOR TORIC IOL AND APPLICABILITY TO A BROADER POPULATION

4.1 ALCON-SPONSORED STUDIES WITH RESTOR TORIC CONDUCTED OUTSIDE THE US

In addition to Clinical Study C-09-036, the ReSTOR Toric IOL was included in four studies conducted outside of the United States (J-10-050, M-09-051, M-09-052, and RDG10-269). Data from these studies will not be used to support labeling claims in the United States.

Study J-10-050 was a single-arm, open-label multi-center study conducted in Japan to support the regulatory approval of the product in that country. The effectiveness outcomes from this study were consistent with the primary outcomes of Clinical Study C-09-036. Studies M-09-051, M-09-052, and RDG-10-269 were postmarket studies conducted in the European Union and Latin America to provide additional information on the performance of the lens for marketing purposes. These studies did not assess monocular visual acuity (at distance and at fixed near distance), therefore a direct comparison to the primary outcomes of Clinical Study C-09-036 is not possible. However, the binocular visual acuity outcomes evaluated for these three studies were similar in most cases to that of Clinical Study C-09-036.

Overall, results of the studies conducted outside of the United States support a similar benefit to risk profile for the ReSTOR Toric IOL as established in Clinical Study C-09-036. Some differences for IOL misalignment were observed between Clinical Study C-09-036 and the studies outside the US. After evaluation of all findings, the most likely explanation was differences in IOL axis assessment across studies.

In Clinical Study C-09-036, sites in the US used a photographic method and the PALO software specifically designed to assess IOL alignment for IOL axis measurement (see Section 3.5.2). The Japanese study used a non-validated method and an anterior segment OCT for IOL orientation. Specifically, in the US study, two reference positions of the intended axis of the IOL placement axis identified by the study specific web-based ReSTOR Toric calculator were precisely marked and used during surgery for axis alignment. In the Japanese study, investigators visually aligned the lens axis with the target axis provided by the web-based ReSTOR Toric IOL calculator during surgery. The differences in the methods used for IOL placement and axis measurement in the US and Japan clinical studies most likely contributed to the differences in the IOL axis rotation and misalignment results.

Lens rotation in studies M-09-051, M-09-052, and RDG-10-269 was measured using a non-photographic method. Although some subjects in the studies did experience reported lens misalignment, very few subjects required surgical intervention for realignment or had poor visual outcomes. Since photographic images were not required for these studies, it is difficult, or even impossible, to determine from the available data the

actual amount of lens misalignment (including misplacement at surgery and rotation after surgery) experienced to compare to the US misalignment data recorded with photographic images.

Overall, the clinical studies of the ReSTOR Toric IOL conducted in the US, Japan and other countries outside the US did not raise any new concerns with effectiveness or safety, including SSIs due to optical properties and visual distortions/disturbances.

4.2 POSTMARKETING EXPERIENCE WITH RESTOR TORIC

As stated previously, the ReSTOR Toric IOL has been available commercially outside the United States since June 2010. Over 82,000 units of ReSTOR Toric have been sold since product launch through 31 March 2014.

Table 47 summarizes the AE reporting in the postmarketing setting from 01 June 2010 through 31 March 2014. The following information can be noted from these data:

- All adverse event terms had a reporting rate less than 4 reports per 10,000 units sold.
- Most types of adverse events were reported in less than 20 cases.
- Frequently reported adverse events included unexpected post-operative refraction, IOL replacement, and impaired vision.

In summary, the AEs reported from postmarketing experience outside the United States are similar to those observed during clinical development and are generally consistent with known complications associated with cataract surgery following the implantation of a Toric or Multifocal IOL.

Table 47. Adverse Event Reporting Frequencies and Reporting Rates (IOL Models SND1T2*, SND1T3, SND1T4, SND1T5, SND1T6) 1-Jun-2010 to 31-Mar-2014

Adverse Event Terms**	2010	2011	2012	2013	Mar 2014	Total	Reporting Rate***
2642 - Postoperative refraction, unexpected		7	8	12	4	31	3.760
992641 - Lens, replacement of		3	8	7	10	28	3.396
Due to unexpected postoperative refraction			2	1	2	5	0.606
Due to impaired vision			1	1	3	5	0.606
Due to Halo		1	1	1	1	4	0.485
Due to wrong power calculation			1	2		3	0.364
Unknown reason/No information provided		2		1		3	0.364
Due to Diplopia			2			2	0.242
Due to IOL decentration secondary to vitreous protrusion.			1			1	0.121
Due to scratch/marks on the IOL				1		1	0.121
Due to IOL haptics chafing the eye					1	1	0.121
Due to loose zonules/ inadequate zonular support					1	1	0.121
Due to visual disturbances					2	2	0.242
2138 - Vision, Impaired		2	5	6	6	19	2.305
2137 - Blurred vision		5	2		2	9	1.091
3191 - No Code Available		1	4	2	2	9	1.091
Dissatisfied/Difficulty reading			1	2	1	4	0.485
Anterior Cell Growth			2			2	0.242
Depth perception, poor		1				1	0.121
Posterior capsule opacification					1	1	0.121
Vitreous in anterior chamber			1			1	0.121
2140 - Visual Disturbances		2	2	1	4	9	1.091
2227 - Halo		3	1	1	1	6	0.727
992571 - Treatment with medication(s)		1	2	2		5	0.606
1791 - Corneal Edema				3		3	0.364
992564 - Surgical procedure, additional			1	1	1	3	0.364
IOL repositioning due to lens dislocation				1		1	0.121
LASIK					1	1	0.121
IOL implantation completed 24 hours after initial surgery. (Lens was broken on initial surgery day and could not be implanted)****			1			1	0.121
2676 - Diplopia			2			2	0.242
2639 - Capsular Bag tear, Posterior			1			1	0.121
1790 - Corneal Decompensation		1				1	0.121
1845 - Eye injury			1			1	0.121
9916 - Photophobia					1	1	0.121
1932 - Inflammation		1				1	0.121
2643 - Vitrectomy			1			1	0.121

Adverse Event Terms**	2010	2011	2012	2013	Mar 2014	Total	Reporting Rate***
Total	0	26	38	35	31	130	
Reporting Rate / 10,000 units sold	0	15.497	13.717	11.755	44.578	15.771	
Total Sales	1,219	16,777	27,702	29,774	6,954	82,426	

*ReSTOR Toric IOL Model SND1T2 is not included in P040020/S049, but included in this data set due to being part of the ReSTOR Toric family and reported complaints are applicable to the other models within the PMA.
**FDA Patient Codes (multiple codes may be assigned to a complaint report).
***Reporting Rate is calculated per 10,000 units sold.
****One quality complaint/ product problem coded "1069 – Break" was reported for IOL Model SND1T2 from Argentina. The lens was broken / crushed when opened and the surgical facility did not have a back-up IOL. The IOL implantation could not be completed and the patient was brought in the next day for IOL implantation. The surgery to implant the IOL on the second day was coded "Surgical procedure, additional".

4.3 APPLICABILITY TO A BROADER POPULATION

The results of Clinical Study (C-09-036) demonstrate that the safety and effectiveness of the ReSTOR Toric IOL in the astigmatic population is consistent with the previously approved parent ReSTOR IOL and are generalizable to a wider population based on several factors. The comparison of the primary safety and effectiveness and secondary safety results between white and non-white subjects suggests that the ReSTOR Toric IOL is effective in both white and non-white subjects with no unanticipated risks identified in these subpopulations. Age and gender distribution of the subjects in the US and OUS clinical trials are also consistent with the target cataract patient population[2] (Table 48).

In addition, The ReSTOR Toric IOL is commercially available in the European Union, Japan, Australia, Canada, multiple countries within Central and South America, the Middle East, and the Far East. More than 93,000 units of the ReSTOR Toric IOL have been distributed in countries outside of the United States since June 2010. As discussed above, no additional safety concerns have been identified from post market surveillance of complaints received from the commercial distribution of the ReSTOR Toric IOLs outside of US, which represents real-life use in a diverse population.

[2] Gollogly HE, Hodge DO,St. Sauver JL, Erie JC. Increasing incidence of cataract surgery: Population-based study. J Cataract Refract Surg 2013; 39:1383–1389.

Table 48. Demographic Characteristics of Subjects in the US and OUS ReSTOR Toric IOL Clinical Trials

Protocol Number	Study Sites	N	Age Mean±SD (Min,Max)	Gender	Race	Study Description
C-09-036	United States	386	66.91±9.20 (26,86)	F: 62.2% M:37.8%	White: 93.8% African American: 3.6% Asian: 1.3 % Other: 1.3 %	Registration clinical study in the United States
J-10-050	OUS (Japan)	65	66.4±9.9 (35,84)	F: 76.9% M:23.1%	Japanese: 100%	Registration clinical study in Japan
M-09-051	OUS (Spain)	9	67.4±4.85 (61,77)	F: 88.9% M: 11.1%	White: 100%	Competitive product performance evaluation
M-09-052	OUS (Germany, Spain, Venezuela)	44	62.52±7.49 (45,75)	F: 68.2% M: 31.8%	White: 93.2% Hispanic: 6.8%	Market support
RDG-10-269	OUS (France, Germany, G.Britain, Italy, Netherlands, Spain)	108	70.0±8.34 (52,88)	F: 58.3% M: 41.7%	White: 95.4% Black: 0.9% Asian: 2.8% American Indian: 0.9%	Market support

* Demographic data for protocol RDG-10-269 represent the multifocal group (both RESTOR Toric IOL and RESTOR IOL subjects)

5 CONCLUSION

For patients undergoing cataract surgery with preexisting corneal astigmatism ≥ 0.75 D, treatment options are needed that correct aphakia, reduce astigmatism, provide near, intermediate and distance vision with an increase in spectacle independence. To provide this option, Alcon developed a single lens, the AcrySof® IQ ReSTOR® +3.0 D Toric Multifocal IOL by combining 2 clinically studied, FDA approved and globally marketed parent IOL technologies (multifocal and toric) for which safety and effectiveness profiles are well established. The ReSTOR Toric IOL provides patients with the benefits of astigmatism correction as well as near, intermediate and distance vision with an increase in overall spectacle independence following implantation.

The ReSTOR Toric IOL has been available commercially outside the United States since June 2010. Over 93,000 units of ReSTOR Toric have been sold since product launch. The postmarketing experience outside the United States is similar to that observed during clinical development and is consistent with known complications associated with cataract surgery following the implantation of a Toric or Multifocal IOL. The ReSTOR Toric IOL demonstrates a favorable benefit to risk profile for patients presenting with preexisting corneal astigmatism ≥ 0.75D, presbyopia and desire an increase in spectacle independence.

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APPENDIX 1: SUBJECTS WITH MONOCULAR UNCORRECTED DISTANCE VISUAL ACUITY OF WORSE THAN 20/63 AND MONOCULAR BEST CORRECTED DISTANCE VISUAL ACUITY WORSE THAN 20/40 AT VISITS 3, 4 OR 5

Out of a total of 386 subjects implanted with ReSTOR Toric IOLs, 1 subject (C09036(b)(6)) had monocular uncorrected distance visual acuity worse than 20/63 and monocular BCDVA worse than 20/40 in the second implanted eye (Visit 1 and Visit 5), indicating that residual refractive error was not the only contributor to the visual acuity outcomes for this subject.

Subject C09036 (b)(6)

Subject C09036(b)(6) was implanted with ReSTOR Toric IOL model SND1T3 in the second eye. As demonstrated in the clinical data for this subject (Table 49), a number of observations were made throughout the course of the clinical investigation that may have contributed to the visual acuity outcomes in the second implanted eye. At Visit 3, vitreous detachment, which was not related to the investigational lens, was recorded and not resolved. At the same visit, a moderate rating for Keratoconjunctivitis sicca was recorded, and this was also not resolved. At Visit 4, mild age-related macular degeneration was recorded and was not resolved, and in addition, mild retinal pigment epitheliopathy was recorded and was also not resolved. At an unscheduled visit following Visit 4, it was first noted by the PI that the subject may have amblyopia due to visual acuity not improving after cataract surgery. After contacting the Optometrist, amblyopia was confirmed with a diagnosis year of 1993. A diagnosis of amblyopia is documented in the medical history panel and at 12 months (Visit 5).

Alcon's Assessment

Based on a review of the subject's data, the visual acuity outcomes may be multifactorial, and may be attributed to the development of age related macular degeneration, dry eye, retinal pigment epitheliopathy and amblyopia. These findings were not related to the investigational lens.

Table 49. Listing of Selected Assessments for Subjects with UCDVA Worse Than 20/63 and BCDVA Worse than 20/40 at Visit 3, 4, or 5: Subject C09036 (b)(6) , Second Implanted Eye

Eye	Lens Model	Study Day	Visit	UCDVA	BCDVA	Sphere Power	Cylinder Power	Axis	MRSE	IOP	Findings
OD	SND1T3	1	Visit 1	0.70	0.38	-0.75	0.00		-0.75	25	(SLE)Aqueous cell, (SLE)Superficial punctate keratitis
		9	Visit 2	0.68	0.24	-1.00	0.25	25	-0.88	20	(SLE)Aqueous cell
		35	Visit 3	0.72	0.24	-1.00	0.00		-1.00	15	(AE)Vitreous detachment[N], (AE)Keratoconjunctivitis sicca[N], (SLE)Posterior capsule opacification, (FE)Vitreous detachment
		172	Visit 4	0.76	0.28	-1.00	0.00		-1.00	14	(SLE)Posterior capsule opacification, (SLE)Superficial punctate keratitis
		177	Unscheduled								(AE)Age-related macular degeneration[N], (AE)Retinal pigment epitheliopathy[N]
		210	Unscheduled	0.74	0.26	-1.00	0.00		-1.00	12	(SLE)Posterior capsule opacification, (SLE)Superficial punctate keratitis[c], (FE)RPE changes
		231	Unscheduled								(AE)Ocular hyperaemia
				0.60	0.26	-0.75	0.00		-0.75	14	(SLE)Conjunctival hyperemia[c], (SLE)Superficial punctate keratitis
		375	Visit 5	0.76	0.40	-1.00	0.00		-1.00	18	(SLE)Posterior capsule opacification, (FE)Other - Retinal pigment epitheliopathy

Sub. = Subject; (AE) = Adverse Event; (SLE) = Slit Lamp Examination; (FE) = Fundus Examination; (SPCO) = Subjective Posterior Capsule Opacification
(IOLOBS) = IOL Observations;(SURGPROB) = Surgical Problems; IOP = Intraocular Pressure; (POSTCAP) = Posterior Capsulotomy
[c]Clinically Significant SLE or FE finding; † = Serious Adverse Event; [a] = Adverse Device Effect; [N] = Adverse Event not resolved
UCDVA = Monocular Uncorrected Distance Visual Acuity; BCDVA = Monocular Best Corrected Distance Visual Acuity
For SPCO only clinically significant requiring a YAG are shown. There are no subjects with IOL Position Change or Retinal Detail.

Of the 188 subjects implanted with the ACRYSOF ReSTOR Multifocal IOL control (Model SA60D3), there were a total of 4 subjects that had monocular uncorrected distance visual acuity worse than 20/63 and monocular BCDVA worse than 20/40 at study Visits 3, 4, or 5 (subjects C09036 (b)(6), C09036 (b)(6), C09036 (b)(6), and C09036 (b)(6)), indicating that residual refractive error was not the only contributor to the visual acuity outcomes for these subjects.

Subject C09036 (b)(6)

Subject C09036. (b)(6) was bilaterally implanted with the ACRYSOF ReSTOR Multifocal IOL control, and had monocular uncorrected distance visual acuity worse than 20/63 and monocular BCDVA worse than 20/40 in the first implanted eye (at an unscheduled visit following Visit 4 (6 months), and also at Visit 5 (12 months)), and in the second implanted eye (at Visit 4, at an unscheduled visit following Visit 4 (6 months) and at Visit 5 (12 months)), This subject also experienced monocular UCDVA and BCDVA of 20/50 at an unscheduled visit prior to 12 months (Visit 5). The clinical data for this subject is presented in Table 50 (first implanted eye) and Table 51 (second implanted eye).

At Visit 3A (1 month post-operative visit), the Investigator noted clinically significant posterior capsule opacification on slit lamp examination. At a subsequent unscheduled visit, the Investigator noted clinically significant posterior capsule opacification requiring YAG laser capsulotomy. A 3 mm YAG laser posterior capsulotomy was performed. At an unscheduled visit, the subject complained of a central dark spot in the right eye and the Investigator diagnosed cystoid macular edema on fundus examination. The subject was referred to a retinal specialist and treated with prednisolone ophthalmic (Pred forte 1%). Alcon received communication via e-mail from the site stating that at an unscheduled visit on 14-Nov-2012, the neuro-ophthalmologist noted central scotoma apparently secondary to maculopathy and an evaluation of OCT images suggested “foveal retinal nerve fiber layer loss”.

Alcon’s Assessment

Based on the review of the clinical data, in the left eye, there was no clear co morbidity to explain the visual acuity outcomes. In the right eye, the visual acuity outcomes were attributed to the development of maculopathy with associated foveal retinal nerve fiber layer loss. These findings were not related to the Control IOL.

Table 50. Listing of Selected Assessments for Subjects with UCDVA Worse Than 20/63 and BCDVA Worse than 20/40 at Visit 3, 4, or 5: Subject C09036. (b)(6), First Implanted Eye

Eye	Lens Model	Study Day	Visit	UCDVA	BCDVA	Sphere Power	Cylinder Power	Axis	MRSE	IOP	Findings
OS	SA60D3	1	Visit 1	0.18	0.18	0.25	0.50	165	0.50	20	(SLE)Aqueous cell, (SLE)Other - Corneal pigmentation
		7	Visit 2	0.36	0.16	-1.50	0.00		-1.50	15	(SLE)Other - Corneal pigmentation
		47	Visit 3	0.10	0.06	-0.75	0.75	175	-0.38	14	(AE)Posterior capsule opacification, (SLE)Posterior capsule opacification[c]
		74	Unscheduled	0.34	0.20	-0.25	0.75	172	0.13	14	(SLE)Posterior capsule opacification[c], (SPCO)Clinically significant requiring a YAG
		153	Unscheduled								(AE)Visual impairment[N], (AE)Diplopia[N]
		168	Unscheduled	0.42	0.30	-0.75	0.25	150	-0.63	12	(SLE)Other - Corneal pigmentation, (POSTCAP)Yes
		169	Unscheduled								(SLE)Other - Cutis laxa, (FE)Vitreous detachment
		175	Unscheduled								(AE)Foreign body sensation in eyes
		189	Visit 4	0.40	0.20	-0.50	0.75	165	-0.13	13	(AE)Blepharitis, (SLE)Other - Blepharitis, (SLE)Other - Corneal pigmentation
		211	Unscheduled								(AE)Dry eye
											(SLE)Other - Conjunctival hyperaemia, (SLE)Other - Cutis laxa, (FE)Vitreous detachment
		224	Unscheduled								(SLE)Other - Cutis laxa, (SLE)Other - Pinguecula
		266	Unscheduled	0.60	0.40	-1.00	1.00	180	-0.50	13	(SLE)Other - Corneal pigmentation
		273	Unscheduled	0.42	0.38	-0.75	1.00	155	-0.25		(SLE)Other - Corneal pigmentation
		372	Visit 5	0.64	0.40	-1.25	1.50	165	-0.50	16	(SLE)Other - Corneal pigmentation

Sub. = Subject; (AE) = Adverse Event; (SLE) = Slit Lamp Examination; (FE) = Fundus Examination; (SPCO) = Subjective Posterior Capsule Opacification
(IOLOBS) = IOL Observations;(SURGPROB) = Surgical Problems; IOP = Intraocular Pressure; (POSTCAP) = Posterior Capsulotomy
[c]Clinically Significant SLE or FE finding; † = Serious Adverse Event; [a] = Adverse Device Effect; [N] = Adverse Event not resolved
UCDVA = Monocular Uncorrected Distance Visual Acuity; BCDVA = Monocular Best Corrected Distance Visual Acuity
For SPCO only clinically significant requiring a YAG are shown. There are no subjects with IOL Position Change or Retinal Detail.

Table 51. Listing of Selected Assessments for Subjects with UCDVA Worse Than 20/63 and BCDVA Worse than 20/40 at Visit 3, 4, or 5: Subject C09036. (b)(6), Second Implanted Eye

Eye	Lens Model	Study Day	Visit	UCDVA	BCDVA	Sphere Power	Cylinder Power	Axis	MRSE	IOP	Findings
OD	SA60D3	1	Visit 1	0.34	0.16	0.00	0.75	180	0.38	19	(SLE)Aqueous cell
		7	Visit 2	0.18	0.02	-0.25	0.75	180	0.13	16	
		33	Visit 3	0.12	0.06	-0.25	1.00	170	0.25	16	(AE)Posterior capsule opacification, (SLE)Posterior capsule opacification[c]
		60	Unscheduled	0.34	0.12	-0.25	1.00	175	0.25	14	(SLE)Posterior capsule opacification[c], (SPCO)Clinically significant requiring a YAG
		147	Unscheduled								(AE)Scotoma[N]
		154	Unscheduled	0.52	0.40	-0.50	0.75	180	-0.13	13	(SLE)Other - Corneal pigmentation, (POSTCAP)Yes
		155	Unscheduled								(AE)Cystoid macular oedema†
											(SLE)Other - Cutis laxa, (FE)Macular edema[c], (FE)Vitreous detachment
		175	Visit 4	0.70	0.36	-1.50	1.75	163	-0.63	17	(AE)Blepharitis, (SLE)Other - Blepharitis, (SLE)Other - Corneal pigmentation, (FE)Macular edema[c]
		197	Unscheduled								(AE)Dry eye
											(SLE)Other - Conjunctival hyperaemia, (SLE)Other - Cutis laxa, (FE)Vitreous detachment, (FE)Other - Cystoid macular oedema
		210	Unscheduled								(SLE)Other - Corneal pigmentation, (SLE)Other - Cutis laxa, (SLE)Other - Pinguecula
		252	Unscheduled	0.60	0.54	-1.25	0.75	5	-0.88	13	(SLE)Other - Corneal pigmentation
		259	Unscheduled	0.42	0.40	-0.75	1.25	175	-0.13		(SLE)Other - Corneal pigmentation
		358	Visit 5	0.70	0.44	-0.75	1.25	178	-0.13	15	(SLE)Other - Corneal pigmentation

Sub. = Subject; (AE) = Adverse Event; (SLE) = Slit Lamp Examination; (FE) = Fundus Examination; (SPCO) = Subjective Posterior Capsule Opacification
(IOLOBS) = IOL Observations;(SURGPROB) = Surgical Problems; IOP = Intraocular Pressure; (POSTCAP) = Posterior Capsulotomy
[c]Clinically Significant SLE or FE finding; † = Serious Adverse Event; [a] = Adverse Device Effect; [N] = Adverse Event not resolved
UCDVA = Monocular Uncorrected Distance Visual Acuity; BCDVA = Monocular Best Corrected Distance Visual Acuity
For SPCO only clinically significant requiring a YAG are shown. There are no subjects with IOL Position Change or Retinal Detail.

Subject C09036 (b)(6) was bilaterally implanted with the ACRYSOF ReSTOR Multifocal IOL control, and had monocular uncorrected distance visual acuity worse than 20/63 and monocular BCDVA worse than 20/40 in the second implanted eye (at unscheduled visits following Visit 4 (6 months), and at Visit 5 (12 months)), indicating that residual refractive error was not the only contributor to the visual acuity outcomes for this subject. The clinical data for this subject is presented in Table 52 (second implanted eye).

At the 6-month visit, the Investigator noted clinically non-significant vitreous detachment and clinically non-significant blepharochalasis. At a subsequent unscheduled visit, the subject presented with cloudy vision and the Investigator noted a clinically non-significant vitreous detachment and clinically significant retinal detachment on dilated fundus examination. Two days later, a retinopexy (pars plana vitrectomy with membrane striping and gas-fluid exchange, and PRP [Panretinal Photocoagulation]) was performed. The next day the Investigator noted clinically non-significant ectropion, conjunctival hyperemia and aqueous cell, on slit lamp examination, and clinically significant periphery-panretinal photocoagulation at 360 degrees and 90 percent remaining gas in the vitreous cavity on dilated fundus examination. At subsequent unscheduled visits to follow up the retinal detachment/retinopexy, the Investigator noted that the retina was attached 360 degrees on dilated fundus examination.

Alcon's Assessment

Based on the review of the subject's data, the visual acuity outcomes may be attributed to the retinal detachment/ repair. These findings were not related to the control lens.

Table 52. Listing of Selected Assessments for Subjects with UCDVA Worse Than 20/63 and BCDVA Worse than 20/40 at Visit 3, 4, or 5: Subject C09036 (b)(6), Second Implanted Eye

Eye	Lens Model	Study Day	Visit	UCDVA	BCDVA	Sphere Power	Cylinder Power	Axis	MRSE	IOP	Findings
OS	SA60D3	1	Visit 1	0.28	0.10	-0.25	0.50	35	0.00	18	(SLE)Aqueous cell, (SLE)Corneal edema, (SLE)Other - Blepharochalasis
		10	Visit 2	-0.08	-0.06	-0.50	0.50	70	-0.25	13	(SLE)Other - Blepharochalasis
		48	Visit 3	-0.06	-0.10	-0.25	0.00		-0.25	11	(SLE)Other - Blepharochalasis, (FE)Vitreous detachment
		132	Visit 4	0.10	-0.06	0.00	0.00		0.00	9	(SLE)Other - Blepharochalasis, (FE)Vitreous detachment
		199	Unscheduled								(AE)Retinal detachment†
				1.40						4	(SLE)Other - Blepharochalasis, (FE)Retinal detachment[c], (FE)Vitreous detachment
		201	Unscheduled								(AE)Retinopexy†
		202	Unscheduled								(SLE)Aqueous cell, (SLE)Other - Conjunctival hyperaemia, (SLE)Other - Ectropion, (FE)Other - Retinal laser coagulation, (FE)Other - Vitreous disorder
		217	Unscheduled								(SLE)Other - Blepharochalasis, (FE)Other - Retinal disorder
		252	Unscheduled								(SLE)Other - Blepharochalasis, (FE)Other - Retinal disorder
		312	Unscheduled								(SLE)Other - Cutis laxa, (SLE)Other - Pupillary reflex impaired, (FE)Other - Retinal laser coagulation, (FE)Other - Vitrectomy
		370	Visit 5	0.90	0.80	-0.25	0.25	180	-0.13	13	(SLE)Other - Blepharochalasis, (FE)Other - Retinal detachment[c], (FE)Other - Retinal scar

Sub. = Subject; (AE) = Adverse Event; (SLE) = Slit Lamp Examination; (FE) = Fundus Examination; (SPCO) = Subjective Posterior Capsule Opacification
(IOLOBS) = IOL Observations;(SURGPROB) = Surgical Problems; IOP = Intraocular Pressure; (POSTCAP) = Posterior Capsulotomy
[c]Clinically Significant SLE or FE finding; † = Serious Adverse Event; [a] = Adverse Device Effect; [N] = Adverse Event not resolved
UCDVA = Monocular Uncorrected Distance Visual Acuity; BCDVA = Monocular Best Corrected Distance Visual Acuity
For SPCO only clinically significant requiring a YAG are shown. There are no subjects with IOL Position Change or Retinal Detail.

Subject C09036 (b)(6) was bilaterally implanted with the ACRYSOF ReSTOR Multifocal IOL control, and had monocular uncorrected distance visual acuity worse than 20/63 and monocular BCDVA worse than 20/40 in the second implanted eye (at Visit 3), indicating that residual refractive error was not the only contributor to the visual acuity outcomes for this subject. The subject also experienced BCDVA of 20/50 at Visits 1 and 5. The clinical data for this subject is presented in Table 53 (second implanted eye).

Alcon's Assessment

Based on the review of the subject's data, three was no clear reason for the visual acuity outcome, but the subject had PCO and vitreous detachment. None of these findings were related to the control lens.

Table 53. Listing of Selected Assessments for Subjects with UCDVA Worse Than 20/63 and BCDVA Worse than 20/40 at Visit 3, 4, or 5: Subject C09036 (b)(6), Second Implanted Eye

Eye	Lens Model	Study Day	Visit	UCDVA	BCDVA	Sphere Power	Cylinder Power	Axis	MRSE	IOP	Findings
OD	SA60D3	1	Visit 1	0.44	0.44	0.00	0.00		0.00	16	
		11	Visit 2	0.46	0.32	-1.00	0.25	30	-0.88	12	
		36	Visit 3	0.62	0.58	0.50	0.50	95	0.75	12	
		120	Visit 4	0.40	0.30	-0.75	0.00		-0.75	12	(SLE)Posterior capsule opacification
		379	Visit 5	0.44	0.40	-0.75	0.00		-0.75	13	(SLE)Posterior capsule opacification, (FE)Vitreous detachment

Sub. = Subject; (AE) = Adverse Event; (SLE) = Slit Lamp Examination; (FE) = Fundus Examination; (SPCO) = Subjective Posterior Capsule Opacification
(IOLOBS) = IOL Observations;(SURGPROB) = Surgical Problems; IOP = Intraocular Pressure; (POSTCAP) = Posterior Capsulotomy
[c]Clinically Significant SLE or FE finding; † = Serious Adverse Event; [a] = Adverse Device Effect; [N] = Adverse Event not resolved
UCDVA = Monocular Uncorrected Distance Visual Acuity; BCDVA = Monocular Best Corrected Distance Visual Acuity
For SPCO only clinically significant requiring a YAG are shown. There are no subjects with IOL Position Change or Retinal Detail.

Subject C09036(b)(6) was bilaterally implanted with the ACRYSOF ReSTOR Multifocal IOL control, and had monocular uncorrected distance visual acuity worse than 20/63 and monocular BCDVA worse than 20/40 in the first implanted eye (at unscheduled visits following Visit 4 (6 months), and at Visit 5 (12 months)), indicating that residual refractive error was not the only contributor to the visual acuity outcomes for this subject. The clinical data for this subject is presented in Table 54 (first implanted eye).

Alcon's Assessment

Based on the review of the subject's data, the visual acuity outcomes may be attributed to the development of wet macular degeneration/retinal hemorrhage. These findings were not related to the control lens.

Table 54. Listing of Selected Assessments for Subjects with UCDVA Worse Than 20/63 and BCDVA Worse than 20/40 at Visit 3, 4, or 5: Subject C09036 (b)(6), First Implanted Eye

Eye	Lens Model	Study Day	Visit	UCDVA	BCDVA	Sphere Power	Cylinder Power	Axis	MRSE	IOP	Findings
OS	SA60D3	1	Visit 1	0.12	0.12	0.00	0.00		0.00	15	(SLE)Aqueous cell, (SLE)Aqueous flare
		7	Visit 2	0.22	0.26	-0.50	-0.50	120	-0.75	16	(SLE)Aqueous cell
		57	Visit 3	0.26	0.06	-0.50	-0.25	140	-0.63	17	
		162	Visit 4	0.14	0.02	-0.25	-0.25	140	-0.38	15	(SLE)Posterior capsule opacification, (FE)Macular degeneration
		260	Unscheduled								(AE)Age-related macular degeneration†[N]
				1.00	1.00	-0.25	-0.25	140	-0.38	15	(SLE)Posterior capsule opacification, (FE)Macular hemorrhage[c]
		266	Unscheduled								(AE)Intra-ocular injection†
		274	Unscheduled								(AE)Intra-ocular injection†[N]
		370	Visit 5	1.06	1.06	-0.25	-0.25	140	-0.38	14	(SLE)Posterior capsule opacification, (SLE)Other - Conjunctival haemorrhage, (FE)Macular degeneration[c], (FE)RPE changes, (FE)Retinal hemorrhage[c], (FE)Other - Retinal pigment epitheliopathy, (FE)Other - Retinal scar

Sub. = Subject; (AE) = Adverse Event; (SLE) = Slit Lamp Examination; (FE) = Fundus Examination; (SPCO) = Subjective Posterior Capsule Opacification
(IOLOBS) = IOL Observations;(SURGPROB) = Surgical Problems; IOP = Intraocular Pressure; (POSTCAP) = Posterior Capsulotomy
[c]Clinically Significant SLE or FE finding; † = Serious Adverse Event; [a] = Adverse Device Effect; [N] = Adverse Event not resolved
UCDVA = Monocular Uncorrected Distance Visual Acuity; BCDVA = Monocular Best Corrected Distance Visual Acuity
For SPCO only clinically significant requiring a YAG are shown. There are no subjects with IOL Position Change or Retinal Detail.

APPENDIX 2: ACTUAL AND POTENTIAL SECONDARY SURGICAL INTERVENTIONS

Table 55. Case Details of *Potential* Secondary Surgical Interventions: ReSTOR Toric Group

Subject	Eye	Trigger for Potential SSI	Case Details for ReSTOR Toric IOL (n=6 eyes)
(b) (6)	1st 2nd	"Yes" on APPLES question at 6 M	• Moderate halos at 6 M (APPLES) • No SSI performed following medical evaluation • Mild halos at 12 M (improvement via APPLES) • At 12 M: 1st eye = -0.50+0.50x135 2nd eye = plano
	1st	"Yes" on APPLES question at 12 M	• Subject complaint of severe blurry vision at 4 M • SSI of astigmatic keratotomy for residual astigmatism • "Yes" on APPLES at 6 M • SSI of LASIK for residual astigmatism due to lack of success • "Yes" on APPLES at 12 M: severe blurry vision persists • Reported as potential SSI at 12 M • At 12 M: 0.75-0.75x007
	1st	Investigator Assessment of outcome	• No Preoperative calculation errors. • Residual astigmatism reported at 12 M • PI recommended PRK but subject didn't undergo • At 12 M: -0.75+0.75x021
	1st 2nd	Investigator Assessment + "Yes" on APPLES question at 6 M & 12 M	• APPLES complaints of halos, glare, fluttering, & not seeing well in dark. • Inaccurate preop axial length contributed to subject issues as well. • PI recommended LASIK to address but subject didn't undergo • At 12 M: 1st eye = 0.25 (sph) 2nd eye = -1.50+0.50 x44

APPLES Question = "Are you experiencing any symptoms bothersome enough that you would want to have another surgery to reposition or remove the IOL(s), if the lens is determined to be the cause of your visual symptoms?

Table 56. Case Details of *Potential* Secondary Surgical Interventions: Control Group

Subject	Eye	Manifest Refraction @ 12M	Trigger for Potential SSI	Case Details for Control IOL Group (n=4 eyes)
(b) (6)	1st	-1.00+1.00x180	Subject complaint of visual symptoms	• Subject complaint of glare to site @ 6 M • APPLES complaint of moderate blurriness • Posterior vitreous detachment OU and PCO in 1st eye • PI did not recommend SSI unless subject symptoms became intolerable
	2nd	0.00 +0.75x160		
	1st	0.25 (sph)	Subject complaint of visual symptoms	• Severe halos and starbursts at 6 M and 12 M (APPLES) • PI did not recommend SSI and after discussion, subject defers desire for surgery.
	2nd	Plano	"Yes" on APPLES question at 6 M and 12 M	

APPLES Question = "Are you experiencing any symptoms bothersome enough that you would want to have another surgery to reposition or remove the IOL(s), if the lens is determined to be the cause of your visual symptoms?

Table 57. Case Details of *Actual* Secondary Surgical Interventions: Control Group

Subject	Eye	Manifest Refraction @ 12M	SSI Performed	Case Details for Control IOL Group (n=4 eyes)
(b) (6)	1st	0.00+0.50x160	IOL exchange OU	• Yes" on APPLES at 6 M • *Severe* glare, halos *always* at 6 M • Subject intolerance of visual disturbances • Day of SSI: 169 days postop OU* • ReSTOR +3 IOL implanted OU • *Moderate* glare, halos *often* at 12 M (improved frequency and severity)
	2nd	0.25+0.50x017		
	1st	-0.25+0.75x005	IOL exchange OU	• "Yes" on APPLES at 6 M • *Severe* glare, halos, starburst at 6 M • Subject intolerance of visual symptoms and reading distance too close • Day of SSI: 155 days postop OU* • ReSTOR +3 IOL implanted OU • *Moderate* glare, halos and *mild* starburst at 12 M (improved severity)
	2nd	0.00+0.50x175		

*Time to onset for the IOL exchange was relative to the IOL implantation for each eye and resulted in the same onset day.

APPLES Question = "Are you experiencing any symptoms bothersome enough that you would want to have another surgery to reposition or remove the IOL(s), if the lens is determined to be the cause of your visual symptoms?

APPENDIX 3: NARRATIVES FOR SUBJECTS WHO EXPERIENCED SURGICAL PROBLEMS

Narratives for subjects who experienced capsulorhexis tears and anterior capsular tears – ReSTOR Toric

Subject C09036 (b)(6), a 69-year-old Caucasian male, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: right eye (OD) with IOL Model SND1T4 and the left eye (OS) with IOL Model SND1T3. At the operative visit, the subject experienced an **anterior capsule radial tear** in both eyes (OU).

Right eye (OD)

- Preoperatively, the Investigator noted ocular findings of cataract and ecchymosis.
- Cataract surgery was performed on 07-Sept-2011. The Investigator made a 2.3 mm surgical incision at 180 degrees and performed a 5.0 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL Model SND1T4 +15.0 D was implanted using a Monarch III Handpiece with a C cartridge. An "anterior radial tear" occurred during removal of the viscoelastic after IOL implantation, which was reported as an AE that was not related to the IOL.
- After study completion, the Investigator stated that the subject may have had a thinner anterior capsule, predisposing the subject to develop the capsule tear.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was -0.08 logMAR.

Left eye (OS)

- Preoperatively, the Investigator noted an ocular finding of cataract only.
- Cataract surgery was performed on 19-Sept-2011. The Investigator made a 2.3 mm surgical incision at 0 degrees and performed a 5.0 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL Model SND1T3 +14.5 D was implanted using a Monarch III Handpiece with a C cartridge. An "anterior radial tear" occurred during removal of the viscoelastic after IOL implantation, which was reported as an AE that was not related to the IOL.
- After study completion, the Investigator stated that the subject may have had a thinner anterior capsule, predisposing the subject to develop the capsule tear.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.00 logMAR.

Subject C09036 (b)(6), a 76-year-old Caucasian male, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: left eye (OS) with IOL model SND1T4 and right eye (OD) with IOL model SND1T3. At the operative visit, the subject experienced an **anterior capsule radial tear** in the right eye.

- Preoperatively, the Investigator noted ocular findings of cataract and retinal pigmented epithelium (RPE) changes in the right eye.

- Cataract surgery was performed on 26-Sept-2011. The Investigator made a 2.4 mm surgical incision at 180 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T3 +23.5 D was implanted using a Monarch III Handpiece with a C cartridge. An "anterior radial tear" occurred during removal of the viscoelastic after IOL implantation, which was reported as an AE that was not related to the IOL.
- After study completion, the Investigator confirmed that the anterior capsular tear was not related to the IOL, and alternative etiology was not provided.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.00 logMAR.

Subject C09036 (b)(6), a 72-year-old Caucasian male, was bilaterally implanted with the ReSTOR Toric lens following cataract removal: left eye (OS) with IOL model SND1T4 and right eye (OD) with IOL model SND1T3. At the operative visit, the subject experienced an **anterior capsule radial tear** in the left eye (OS).

- Preoperatively, the Investigator noted an ocular finding of cataract only in the left eye.
- Cataract surgery was performed on 26-Sept-2011. The Investigator made a 2.2 mm surgical incision at 0 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T4 +16.5 D was implanted using a Monarch III Handpiece with a D cartridge. An "anterior radial tear" occurred during removal of the viscoelastic after IOL implantation, which was reported as an AE that was not related to the IOL.
- After study completion, the Investigator confirmed that the anterior capsular tear was not related to the IOL, and alternative etiology was not provided.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was - 0.06 logMAR.

Subject C09036 (b)(6), a 71-year-old Caucasian female, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: right eye (OD) with IOL model SND1T5 and left eye (OS) with IOL model SND1T4. At the operative visit the subject experienced a **capsulorhexis tear** in the left eye (OS).

- Preoperatively, the Investigator noted ocular findings of cataract, arcus and anterior vitreous floaters, and vitreous detachment in the left eye.
- Cataract surgery was performed on 01-Dec-2011. The Investigator made a 2.4 mm surgical incision at 0 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T4 +20.0 D was implanted using a Monarch III Handpiece with a D cartridge. A "capsulorhexis tear" occurred after IOL implantation, which was reported as an AE that was not related to the IOL.

- After study completion, the Investigator confirmed that the anterior capsular tear was not related to the IOL, and an alternative etiology was not provided.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.16 logMAR.

Subject C09036 (b)(6) , a 72-year-old Caucasian male, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: left eye (OS) and right eye (OD) with IOL model SND1T4. At Visit 1 (post-op day 1), the Investigator noted a **small anterior capsular tear** in the left eye (OS).

- Preoperatively, the Investigator noted ocular findings of cataract, arcus, folds in Descemet's membrane, and anterior vitreous floaters in the left eye.
- Cataract surgery was performed on 01-Dec-2011. The Investigator made a 2.6 mm surgical incision at 0 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T4 +24.0 D was implanted using a Monarch III Handpiece with a C cartridge. No surgical problems were noted at the operative visit. On Postop Day 1, the Investigator noted a small anterior capsular tear at the 3 o'clock position, which was reported as an AE that was not related to the IOL. The anterior capsular tear was noted to be related to the surgical procedure; however, the exact time of occurrence/ surgery step was not provided.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.14 logMAR.

Subject C09036 (b)(6) a 57-year-old Caucasian male, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: right eye (OD) with IOL model SND1T4 and left eye (OS) with IOL model SND1T3. At the operative visit, the subject experienced a **capsulorhexis tear** in the left eye (OS).

- Preoperatively, the Investigator noted ocular findings of cataract, arcus, and anterior vitreous floaters in the left eye.

Cataract surgery was performed on 29-Dec-2011. The Investigator made a 2.6 mm surgical incision at 0 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T3 +12.0 D was implanted using a Monarch III Handpiece with a C cartridge. A "capsulorhexis tear" occurred after IOL implantation, which was reported as an AE that was not related to the IOL.

- After study completion, the Investigator confirmed that the capsulorhexis tear was not related to the IOL, and an alternative etiology was not provided.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.02 logMAR.

Subject C09036 (b)(6), a 78-year-old African American male, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: left eye (OS) with IOL model SND1T4. At the operative visit for the right eye, the subject experienced a **capsulorhexis tear** secondary to the breaking of the IOL haptic following implantation of a ReSTOR Toric IOL (Model SND1T3).

- Preoperatively, the Investigator noted an ocular finding of cataract only in the right eye.
- Cataract surgery was performed on 13-Dec-2011. The Investigator made a 2.5 mm surgical incision at 180 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T3 +20.0 D was implanted using a Monarch III Handpiece with a D cartridge. Following IOL implantation, the subject experienced a capsulorhexis tear secondary to the breaking of the IOL haptic. The ReSTOR Toric lens was explanted from the right eye, and the subject was successfully implanted with a non-study IOL (Model MN6AD1). The capsulorhexis tear was reported as an AE, which was related to the IOL.
- The haptic breakage was reported as a device deficiency. The subject continued participation in the study for the left eye.

Narratives for subjects who experienced capsulorhexis tears and anterior capsular tears – Control

Subject C09036 (b)(6), a 76-year-old Caucasian female, was bilaterally implanted with the **Control lens** following cataract removal: right eye (OD) and left eye with IOL Model SA60D3. At the operative visit, the subject experienced a small **anterior capsular extension** in the right eye (OD).

- Preoperatively, the Investigator noted ocular findings of cataract, adipose tissue prolapse, dry eye syndrome, dermatochalasis and reduced tear meniscus in the right eye.
- Cataract surgery was performed on 21-Sept-2011. The Investigator made a 2.4 mm surgical incision at 170 degrees and performed a 5.5 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SA60D3 +20.5 D was implanted using a Monarch III Handpiece with a D cartridge. The Investigator noted that an anterior capsulorhexis extension occurred during capsulorhexis, prior to phacoemulsification.
- The Investigator did not consider the anterior capsular tear to be an AE and hence it was not reported as such. The Investigator further confirmed via email communication received on 3-Dec-2013 that the capsulorhexis extension was not related to the IOL.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.00 logMAR.

Narratives for subjects who experienced zonular damage

Subject C09036 (b)(6), a 72-year-old Caucasian female, was bilaterally implanted with the **ReSTOR Toric lens** following cataract removal: right eye (OD) and left eye (OS) with IOL Model SND1T3. At the operative visit, the subject presented with **partial zonular dehiscence** in the right eye (OD) that required implantation of a ReFORM® capsular tension ring.

- Preoperatively, the Investigator noted ocular findings of cataract and pseudoexfoliation.
- Cataract surgery was performed on 14-Dec-2011. The Investigator made a 2.4 mm surgical incision located at 180 degrees and performed a 5.0 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SND1T3 +23.5 D was implanted using a Monarch II Handpiece with a C cartridge. The Investigator noted mild partial zonular dehiscence after IOL implantation and a capsular tension ring was placed.
- The subject did not experience IOL tilt or decentration. BCDVA at Month 12 was 0.10 logMAR.

Subject C09036 (b)(6), a 66-year-old Caucasian male, was bilaterally implanted with the **Control lens** following cataract removal: left eye (OS) and right eye (OD) with IOL Model SA60D3. At the operative visit, the subject presented with **inadequate zonular support** in the right eye (OD) that required implantation of a ReFORM® capsular tension ring.

- Preoperatively, the Investigator noted an ocular finding of cataract only.
- Cataract surgery was performed on 07-Sept-2011. The Investigator made a 2.2 mm surgical incision located at 180 degrees and performed a 5.0 mm anterior capsulorhexis. Viscoat OVD was used during the surgical procedure, and IOL model SA60D3 +21.00 D was implanted using a Monarch III Handpiece with a D cartridge. The Investigator noted zonular weakness during the unfolding of the IOL, and a capsular tension ring was implanted. The zonular weakness was not related to the IOL.
- On Postop Day 1, the IOL was decentered by 2 mm. The Investigator noted that the nasal zonules were absent. Without the placement of the capsular tension ring, the IOL would likely have been decentered more than 2 mm. BCDVA at Month 12 was 0.00 logMAR.